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TOXEMIA OF PREGNANCY

C. Paul Hodgkinson, M.D.*

Until we know the cause and etiological mechanism whereby toxemia of pregnancy comes about, the definition, classification and treatment must be along emperic lines. It remains the perennial challenge to obstetricians and cognate workers and so long as knowledge remains inadequate, clinical emphasis must be placed on treatment. Re-evaluation of the management of toxemia, therefore, rightfully is a focal point for every obstetrical program because toxemia of pregnancy is still one of the great killers of pregnant women and their babies. It is a complication of 1 to 3% of all pregnancies, involving primipara three times as often as multipara. It has been estimated that toxemia is responsible for approximately 30,000 stillbirths each year and undeterminable number of premature deliveries.

Because the classification of toxemia must be based upon clinical observations of hypertension, proteinuria and edema, symptoms common to other diseases, the diagnosis will sometimes be vague and uncertain. Nevertheless, the division into A, diseases not peculiar to pregnancy, and B, diseases dependent upon and peculiar to pregnancy, is a convenient classification for the clinician. It must be stated that, at times, this distinction may be difficult.

Recently, among the staff of our department there was contentious controversy about the diagnosis of the disease process involving a patient aged 43, pregnant for the sixth time. She was admitted to the hospital during the twenty-first week of pregnancy because of the sudden onset of hypertension ranging in the average of 180 mm of mercury systolic and 110 diastolic, albuminuria amounting to 4.5 grams per 24 hours, and generalized edema. Laboratory studies were all within normal limits except for urinalysis which showed in addition to proteinuria, the presence of red blood cells in considerable quantity. The blood showed no evidence of nitrogen retention, including uric acid. Although no uniformity of the diagnosis was forthcoming, all agreed that continued hospitalization and bed rest were indicated. Under this program she improved, and after six weeks the blood pressure averaged 140 mm of mercury systolic and 85 diastolic, albuminuria diminished to a 24 hour excretion of less than 1 gram, and the edema, particularly of her face, largely vanished.

The staff, including those of the cognate medical services, agreed that the diagnosis was most likely acute glomerulonephritis, and recommended continued hospitalization until the termination of pregnancy. A distinguished obstetrician visited the hospital at this time and the details of the patient's condition were presented to him together with our diagnosis. He disagreed and stated that in his opinion the patient was suffering from severe preeclampsia.

The patient left the hospital against our advice and was not seen again until she responded to a telephone call to come for observation. The symptoms of hypertension, albuminuria, and edema were still present. Hospitalization was again enforced. Her blood pressure averaged 220 mm mercury systolic and 110 diastolic. The 24 hour

*Gynecologist-Obstetrician-in-chief, Department of Gynecology and Obstetrics, Henry Ford Hospital.

excretion of albumin in the urine measured 2 grams, and edema of the dependent type was observed. Laboratory studies showed the urine to be free of red blood cells, and there was no nitrogen retention in the blood except for uric acid which was elevated to 6 mgm per 100 cc. Under observation the uric acid continued to climb and reached a maximum of 11 mgm per 100 cc of blood. At about thirty-two weeks gestation intrauterine infant death occurred and one week later, labor commenced spontaneously. When discharged 10 days after delivery the blood pressure ranged in the high normal level, the urine contained a trace of albumin, and the edema had vanished.

The final diagnosis was acute glomerulonephritis with superimposed severe preeclampsia.

Classifications:

Preeclampsia is divided into two degrees of severity — mild and severe, and eclampsia is divided into convulsive and non-convulsive.

Preeclampsia has been defined as toxemia which arises after the twenty-fourth week of gestation characterized by a systolic rise in blood pressure to 160 mm of mercury, and a diastolic rise to 100. The 24 hour urine excretion contains less than 0.6 gram of protein, and edema is slight or absent.

Severe preeclampsia is the same condition characterized by higher elevation of blood pressure, excretion of larger quantities of protein and obvious edema. This inane differentiation of preeclampsia into two grades has about the same degree of meaning as do the yellow and red lights of our traffic signals in Michigan, and if ignored, about the same result. The importance of the differentiation lies in the warning significance to the obstetrician. Although mild preeclampsia is a phase of the disease in which the obstetrician has moderate leeway for the employment of conservative therapeutic measures on a home treatment basis, severe preeclampsia demands immediate bed rest, preferably in a hospital and the most cautious care. In each instance the objective is to modify the intensity of the symptoms so as to prevent the development of eclamptic convulsions, the highly lethal phase of the disease. Committees on Maternal Mortality reach their highest degree of vituperation when obliged to study a death from eclampsia when the records show gradual progression through the phases of mild to severe preeclampsia to actual eclampsia and death without evidence of the obstetrician having recognized the significance of the warning signs and not having instituted appropriate therapy.

Pathology:

Probably no better reason exists for dividing toxemia into preeclampsia and eclampsia than comes from a study of pathology. In preeclampsia, necropsy studies have been most unrewarding. Few, if any pathologic lesions have been recognized which can be considered specific.

Although no precise pathological lesion has been identified there has been rather general acceptance of the functional and structural associated changes present in the preeclamptic phase of the disease. Vasospasm, particularly arteriolar spasm, appears to be common denominator present in all visceral pathologies. Garber[1] stated that these changes in the blood vascular system are evidence of a widespread under-lying

abnormal vasopressor activity or arteriospasm. In effect, according to Garber, this change causes decreased blood flow, anoxemia, and increased capillary permeability with edema and stasis leading to thrombosis, hemorrhage, ischemia and necrosis. Unfortunately, these last four: thrombosis, hemorrhage, ischemia and necrosis are pathologic findings in eclampsia and not preeclampsia. It is a clinical fact that preeclampsia, no matter how severe, fails to cause these lesions; while eclamptic convulsions, no matter at what level of blood pressure they may occur, frequently cause them.

Some observations of interest were recently reported by Pollack and his group[2] showing the results of kidney biopsy performed in patients having preeclampsia. They recognized three lesions of which one was completely reversible, one partially reversible, and one permanent.

The reversible lesion occurred in the uncomplicated preeclampic patient and was characterized by swelling of the glomerular tuft, widening of the basement membrane from swelling which involved the basement membrane, the endothelium and the epithelium, many narrow capillary lumens, vacuoles in the glomerular tuft, and no evidence of a mucopolysaccharide over the basement membrane. In this group of patients the glomeruli appeared large, and crowded Bowman's capsule. These lesions were completely reversible, and after delivery, re-biopsy showed absence of swelling of the glomerular tuft and return of the thin delicate basement membrane.

The second group of patients, partially reversible, showed the same findings plus sclerotic thickening of the basement membrane. After delivery all findings disappeared except sclerosis of the basement membrane.

The third group of patients, which showed permanent disease pathology, was composed of patients having known vascular sclerosis. Most had diabetes. Here sclerosis was permanent.

Pollack differentiated the findings in the preeclamptic group as changes within the basement membrane and not a deposit over the membrane as was observed by Fahr, Bell, Sheehan and others in patients having eclamptic convulsions.

The pathology in convulsive eclampsia, in contrast, is definite, varied and widespread. In turn, pathologists have directed attention to the kidneys, liver, brain, and other viscera recognizing thrombosis, hemorrhage, ischemia, and necrosis as the basic pathologic lesion.

The cause still remains obscure and each has his pet theory. Perhaps sufficient importance has not been given to the pathogenic potentialities of the convulsive act per se, which is an acute catabolic mechanism. In 1949 Dillon and Schmitz[3] reported afibrinogenemia following fulminating eclamptic convulsions, a condition which never occurs unless actual tissue injury is incurred. Realizing that fibrinogen depression is preceded by the fibrinogen-fibrin conversion to insoluble fibrin gel, and possible embolism, gives credence to this pathogenic mechanism as a potential lethal factor. Moreover, there appears to be no reason why the mucopolysaccharide coating over the basement membrane of Bowman's capsule, as observed by Bell[4] and others[5], could not be adherent fibrin gel. That convulsions do cause fibrinogen depression was ob-

served from the fibrinogen profile obtained from a male who developed convulsions after injection of a drug. (Fig. No. 1)

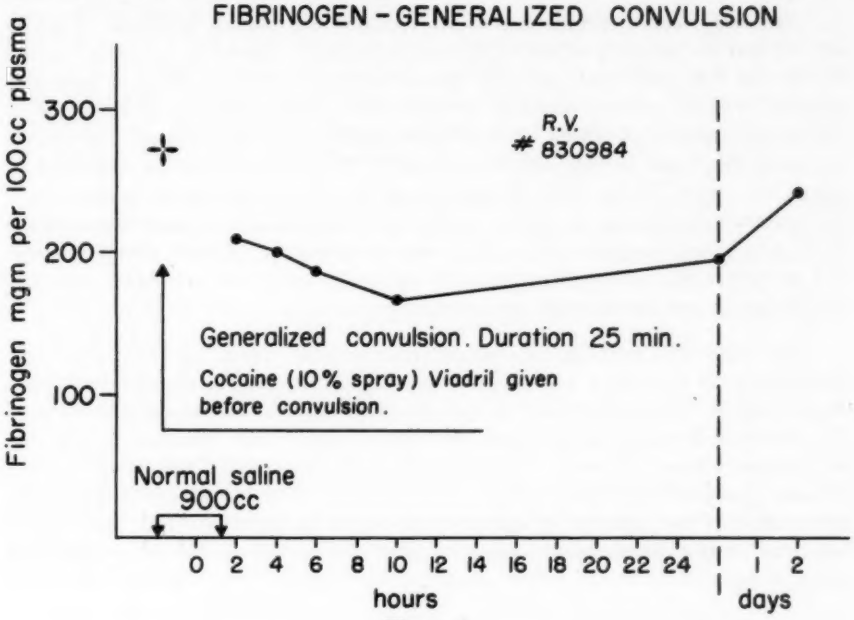

Figure 1

Treatment:

As stated by Cosgrove[6], "lacking then a guide of any established knowledge of etiology and pathogenicity, the management and treatment of the late toxemias of pregnancy remain on exactly the same basis upon which our fathers established it. It presents three phases: prophylaxis, treatment of symptoms, and termination of pregnancy."

Prophylaxis against the development of toxemia is a modern obstetric sophism. How can the disease be prevented when there is no knowledge of etiology? Can any obstetrician rightfully state before a patient undertakes a pregnancy, that she will not develop toxemia? Until we know what destines a patient to develop toxemia, how can we tell her how to avoid it?

On the other hand clinical experience has shown that assiduous attention to the details recommended by good obstetrical teaching will prevent, in most instances, mild preeclampsia advancing to severe preeclampsia, and severe preeclampsia to convulsive eclampsia. This is the practical aim of modern obstetrics and is the reason for our constant obligation to continuously re-evaluate the problem by incorporating into the tried basic plans of therapy, new modalities of treatment .

Because of the proclivity of the pregnant patient to retain excessive quantities of sodium and water, manifested clinically as unusual weight gain, assiduous prenatal

care has as its objective: the detection, control or elimination of excessive weight gain, edema, and elevation in blood pressure.

Commonly related sodium and water retention are clinical problems of major concern, and the standard efforts of prevention include: restriction of sodium intake to less than 0.5 grams each day and relative limitation of fluid intake in quantities sufficient to insure urinary output of 2000 cc daily. Sudden increase in body weight and the development of edema occur in some patients after the slightest indiscretion. Treatment then must include efforts to eliminate the retained excessive quantities of sodium and water. To the basic plan of therapy must be added the use of such drugs as ammonium chloride for its diuretic effect, oral administration of magnesium sulfate for its dehydrating purgative effect, and sometimes mercurial diuretics. These methods have withstood the test of time, and although their limitations are recognized, this plan of therapy remains standard for preeclampsia.

New drugs and methods are available for appraisal. These are based upon new pharmacological knowledge and new physiochemical concepts. Clinical trial has been limited. Up for consideration are 1. diuretic of the carbonic anhydrase inhibitor type (Diamox) which selectively eliminates the cations, sodium and potassium, in addition to increased volumes of water: 2. cation exchange resins which selectively interfere with the absorption of cations, sodium and potassium; 3. the evaluation in pregnancy and toxemia of the influence of adrenocorticotrophic hormone (ACTH) and adrenal corticoids: and 4. determination of the clinical effectiveness of the newer antihypertensive drugs.

Carbonic Anhydrase Inhibitor:

Diamox is a potent carbonic anhydrase inhibitor. It functions by inhibiting the conversion of carbon dioxide and water to carbonic acid in the renal tubular cells. With a deficiency of hydrogen ions in the glomerular filtrate, the other cations, sodium and potassium, take hydrogen's place in the buffer systems of the glomerular filtrate and are excreted. As the result the urine becomes highly alkaline. Ashe and his group[7] reported favorable results using an intermittent treatment schedule consisting of 250 mgm daily for 5 days followed by a drug-free interval of two days. This schedule was continued until delivery. They reported no attributable fetal mortality nor maternal side-effects in 100 patients treated, and only 9 patients failed to respond.

Excessive and continuous use of Diamox will cause an inordinate loss of fixed base and result in decreased blood pH, hyperchloremic acidosis from retention of the chloride ion, and decreased CO_2 concentration resulting from excessive ventilation and failure of production of carbonic acid.

Our experience with Diamox corresponds with that reported by Ashe and his group. We also observed rapid weight loss during the time of administration of Diamox. When the drug was discontinued, the patients rapidly regained the weight previously lost. We found it difficult to discontinue the drug during pregnancy. The concomitant use of ammonium chloride during Diamox therapy should be avoided because the chloride ion may augment the tendency to acidosis. Antihypertensive drugs may be given in conjunction with Diamox.

Synthetic Resins:

Synthetic ion exchange resins have been used to some extent during the past five years in an attempt to control sodium retention and excessive water storage. They function by exchanging one ion for another. Two general types have been developed: anion resins which exchange one negatively charged ion for another negatively charged ion, and cation resins which exchange positively charged ions. In obstetrics most interest centers upon the cation, sodium, and there are two resins commercially available which function to remove sodium ions: (1) the sulphonic and (2) the carboxylic.

The ion exchange resins are mentioned, not because they possess any practical value in the treatment of toxemia of pregnancy (because they apparently have little or none,), but because of the attractive physiochemical mechanism whereby they function. For the present, let it suffice to recognize their potential vuale and be prepared to consider the problem afresh should more specific and efficient preparations become available in the future.

Adrenocorticotrophic Hormone and Adrenal Corticoids:

The similarity between the symptoms of toxemia of pregnancy and the physiological effects of ACTH and/or cortisone are striking. In non-pregnancy ACTH and/or cortisone can be expected to produce sodium retention, potassium excretion, elevated blood uric acid, increased excretion of 17-ketosteroids and occasionally albuminuria and hyperglycemia. Also frequently observed are hypertension, sudden weight gain, and edema. A shift of fluid from the extracellular to the intracellular compartment may occur. Many of these changes occur in pregnancy.

The relationship of adrenocorticosteroid metabolism to normal and toxemic pregnancies has been studied by several groups. Lloyd[8] noted increased excretion of poorly watersoluble corticoids in the urine of patients suffering from toxemia of pregnancy. Others[9] noted a toxemia-like condition in animals following administration of DOCA and a high salt diet.

Our group[10] made an effort to evalute the tolerance of the pregnant patient and her unborn infant to ACTH and cortisone. It was our opinion that the hormones neither significantly altered the course of toxemia of pregnancy nor caused its development.

The most striking observation was the apparent increased tolerance of the pregnant patient to ACTH and/or cortisone. None of the patients studied showed changes of significant deviation from normal in plasma potassium, plasma, chlorides, plasma sodium, blood sugar, and uric acid. The cause for increased tolerance to ACTH and/or cortisone during pregnancy is not known.

One must remember that these are potent drugs, and like new cars, their "horsepower" or potency is stepped up as the drugs are better prepared and new ones introduced. We are still concerned that the fetus in utero possibly does not withstand, with the same apparent degree of impunity as the mother, the maternal administration of these drugs. Recently five patients under our observation in whom ACTH and/or cortisone was administered during pregnancy suffered intrauterine fetal death concomitant with hormone therapy. In several instances this tragic event was unexpected and it was difficult not to impute ACTH and/or cortisone.

Antihypertensive Drugs:

In severe preeclampsia, impending convulsions threaten the patient and challenge the obstetrician. Increasingly severe hypertension, proteinuria and edema are the cardinal symptoms.

In severe preeclampsia, as in eclampsia, the objective of therapy is to prevent convulsions. With early delivery the ultimate objective, pre-delivery management has as its obligation, the responsibility of arresting and turning the aberrent physiological processes toward normal homeostatic levels. Evacuation of the uterus can then be accomplished with safety. In this phase, hypertension is the chief threat and arteriolar spasm the chief physiological deviation.

Hemodynamic factors concerned with arterial pressure are four in number: 1. cardiac output and cardiac force, 2. blood volume, 3. viscosity of the blood, and 4. peripheral resistance. These factors are under two types of control: neurogenic and humeral. In pregnancy, and in toxemia, the factors showing greatest deviation from normal are blood volume and increased peripheral resistance. A priori reasoning suggests that drugs useful for the treatment of critical hypertension of toxemia should reduce blood pressure without compromising blood flow through vital organs. Granted, that treatment is directed toward a symptom and not a cause, and drastic, precipitous hypotension may be as dangerous as hypertension, the stark fact remains that most deaths from toxemia result from convulsions, cerebral hemorrhage, left heart failure, and renal failure. Anti-hypertensive drug therapy has as its objective: control and not cure.

The drugs available can be classified into four groups acording to their main point of action:

Group No. 1 Central nervous system — probably the hypothalamus

1. hydrazinophthalazine (Apresoline)
2. veratrum veridi
3. rauwolfia serpentina

Group No. 2 Ganglionic Blocking agents

2.1 tetraethylammoniumchloride, TEAC
2.2 ansolysis
2.3 hexamethonium
2.4 spinal anesthesia

Group No. 3 Adrenergic blocking

3.1 Adrenolytic
  3.1 regitine
  3.2 benzodioxane
3.2 peripheral acting — nerve endings, sympatholytic
  3.2.1 priscoline
  3.2.2 dibenamine

Group No. 4 Miscellaneous

4.1 morphine — antidiuretic and respiratory depressant
4.2 barbiturates — decrease cerebral blood flow
4.3 magnesium sulfate, (parenteral) increase cerebral blood flow and an anticonvulsant

The ideal drug for use in preeclampsia should have the following attributes:

1. lower blood pressure
2. maintain cardiac output
3. not effect cerebral blood flow
4. vasodilate
5. not effect renal blood flow
6. not be antidiuretic
7. not produce orthostatic hypotension
8. its use should be compatable with the use of other drugs
9. maintain patient alertness
10. have few side effects
11. leave no residual effects
12. leave no fetal side effects
13. have versatility of administration: I.V., Oral, I.M.
14. anticonvulsant
15. be capable of both rapid and gradual effects

Using these critera, the drugs most useful for the treatment of preeclampsia are: hydrazinophthalazine (Apresoline), veratrum veridi and its purified extracts, rauwolfia serpentina, and its alkaloids, and magnesium sulfate, (parenteral).

Hydrazinophthalazine:

(Apresoline) causes mild tachycardia, is a vasodilator, reduces blood pressure, increases cardiac output, has relatively few sides effects, increases renal and cerebral flow, and does not change the blood volume. It is effective when administered by mouth and can be given intravenously to bed patients when prompt action is necessary. It is a valuable drug and appears to occupy the "number one" spot at the present time for treatment of hypertension of toxemia.

Veratrum Veridi:

This drug conforms to all the critera except for the disadvantage of causing more side effects. It appears that veratrum can be used to its greatest advantage as an emergency drug in situations characterized by dangerous hypertension. Veratrin extract given intravenously in an initial dose of 0.5 mgm augmented when necessary at half hour intervals by the administration of an additional 0.1 mgm will generally effect a prompt fall in blood pressure to less dangerous levels. The associated vagal stimulation causes slowing of the heart rate and nausea, which action can be negated through the administration of atropine. The drug is also effective when administered intramuscularly and orally. During intravenous administration, blood pressure should be recorded at 10 minute intervals and sudden extreme degrees of depression of arterial blood pressure should be avoided.

Rauwolfia serpentina:

This is a good drug which has the attributes of vasodilatation and mild sedation. Its disadvantage is its slow action. In toxemia rauwolfia is used most frequently in mild preeclampsia when it is given by oral administration to patients on a restricted ambulatory schedule. Here the mild sedative and hypotensive actions can be used to advantage.

Magnesium sulfate:

Magnesium sulfate when given orally is a dehydrating purgative and is useful

in toxemia of pregnancy to aid in mobilization of extracellular body water. When given parenterally the pharmacological actions of magnesium sulfate are anticonvulsive and sedative. In toxemia of pregnancy its parenteral use is most effective for prevention impending convulsions. Magnesium sulfate when administered parenterally causes slight decrease in heart rate, mild vasodilatation, and slight lowering of the blood pressure. It does increase cerebral blood flow and renal blood flow. In these actions it is inferior to hydrazinophthalazine, veratrum and rauwolfia, but it can be in conjunction with these drugs for its synergistic action.

The other drugs mentioned have limited use in toxemia of pregnancy and some have definite disadvantages. Barbiturates lower blood pressure but they seriously reduce cerebral blood flow, oxygenation of the brain, and they do not relieve vasospasm. Morphine also reduces cerebral blood flow. The ganglionic blocking agents cause serious postural hypotension and the adrenergic drugs are most useful as diagnostic agents in patients suspected of having pleochromocytoma.

Conclusion:

It is important to remember the only cure for toxemia of pregnancy is termination of pregnancy as Cosgrove (6) stated. It is necessary to remember that it is the toxemic state that is inimical to both mother and fetus, and that termination of the pregnancy is most certainly salutary for the mother and probably so for the infant. For the infant the chance for survival from the state of prematurity is many times greater than is continued intrauterine survival should severe preeclampsia be prolonged or eclamptic convulsions intervene.

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MEDICAL RESPONSIBILITY AND AUTHORITARIANISM

EUGENE J. ALEXANDER, M.D.*

(Foreword: The pleasures of group practice, such as we have at Henry Ford Hospital, are several; and one which may not readily be apparent to an outsider, is the uniquely satisfying and educational experience of daily luncheon conversation with one's friends and associates. Our topics may be as varied as at any luncheon table, but often they are directly related to the practice of medicine. For instance, what began as a facetious discussion between Dr. Schimek, Dr. Davidson, and Dr. Dill[1], about a "graph" to compare "What the doctor thinks he knows," with "What he actually knows," at different phases in his medical career, provoked the quite serious comment from Dr. Dill that, at the Ford Hospital, we can keep aware of the scientific advances in medicine, simply by listening, at lunch, to what our friends — specialists in fields other than our own — have to say. With this, I heartily agree. And what a pleasant way in which to learn! The fine art of conversation may be dying out in the living room, drowned perhaps by alcohol and the din of the television set in the background; but conversation which is stimulating, thought-provoking and informative, while at the same time being enjoyable, as listener or participant, still lives in the dining room on the 17th floor of the new Clinic building of the Ford Hospital. Personally, whenever I have been mulling a problem over in my mind, I introduce it at lunch, and usually get it clarified. May I here present a sample?)

I had felt troubled after reading an eloquent and persuasive discussion by a psychologist, George A. Kelly[2], to the effect that the medical profession does not do good psychotherapy because it is handicapped by assuming "medical responsibility" for the patient. The implication is that responsibility and authority are inseparably linked, and that authoritarianism is inimical to growth. Individuals may seem indecisive and appeal to us for direction, yet they are more "autonomous" than they appear. They could make those decisions, with reasonably good judgment, if we did not go beyond our position as doctor and cut their waverings short, by telling them what to do. By so doing, we foster their dependence and immaturity, and hinder personality growth.

When I had described this viewpoint, those present were quick to rise to the defense of the medical profession. We do not assume authority over the patient. It is thrust upon us. The patient and his family appeal to the doctor, almost as if he were the one who made the patient sick: "What are you going to do about it, doctor?"

Dr. McIntyre commented that, indeed, this attitude of laying the problem in the doctor's lap is often present. However, early in his psychotherapeutic relationship with an individual patient, he makes it clear that it is the patient who will be "doing" something. What may be wise or healthful for the patient to "do" could be discussed, but the decisions to act and the responsibility for carrying out the actions would remain with the patient. Dr. McIntyre told of an incident which had helped him to define, in his own mind, the relative role of doctor and patient. Early in his medical training, while rotating through the Dermatology service, he had once felt cornered by a patient's demand that he "do something." Dr. Menagh had helped him escape the feeling of

*Division of Psychiatry.

being pressured by the patient, by commenting, "I never grew a single cell on anybody's hide but my own."

This is a quotable restatement of Dr. Ambrose Pare's famous observation, "I dress the wound; God heals it." We tell the patient how he may aid nature in curing himself, but we need feel no sense of frustration, of personal failure, or of insult, if the patient chooses not to aid, but to hinder nature.

However, while we may not intend to assume an authority over the patient, we may unwittingly do so. I reminded the group that, for example, we may word our advice as commands. We say, "You must not smoke." Unless the patient asks us, we may not explain the exact degree of harm (as in Buerger's disease) or the exact degree of discomfort (as in the scratchy throat about which the anxious patient is complaining) which may result from failure to follow our advice. Dr. Noshay agreed, but felt that experience teaches us to avoid that error. The longer he practices, the more he finds himself explaining the reasons for the suggestions he makes, thus leaving the patient free to choose, with full awareness, whether the gain, on the one hand, is worth the inconvenience, on the other hand, connected with following the doctor's advice.

If the wise doctor, as each of us present assumes himself to be, consciously avoids authoritarianism, then how are we to explain the rebellious feelings we get when the patient starts telling us how he wants to be treated? I remember hearing a doctor say that if a patient asks him for a specific one of the new tranquillizing drugs, it so annoys him that he is certain to prescribe a different one. When a new patient begins his relationship with me by asking for electric shock treatment, I feel a prejudice against that treatment for that patient arising within me. Dr. Noshay told of a patient to whom he gave histamine treatment for multiple sclerosis, not when the patient demanded it, but only later, after it was made clear that he, not the patient, had ordered it.

Dr. Dickson summed it up by remarking that the patient's request for a specific treatment should not, in logic, constitute a contraindication to the treatment; yet we seem to feel that it does. This sounds like a jealous guarding of authority, as if we have to show him who's boss.

Dr. Dickson went on to make the point that authority has its usefulness. He told of a small child who, meeting a permissive adult, became more and more anxious until the adult finally wisely said, "No." Anxiety is quieted by strong leadership.

As I left the luncheon table, I was stimulated by Dr. Dickson's last point to remember the time when I had my acute appendicitis. I had somewhat atypical symptoms, so that to me the diagnosis seemed uncertain. How comforted I felt, when Dr. Fallis, without a trace of hesitation or apparent doubt (I wonder how much he felt internally) announced that operation was necessary. Yet this decisiveness, necessary in a good doctor, is not the same thing as authoritarianism. Had I been a Christian Scientist, and refused the surgery, I feel sure that Dr. Fallis would have been equally decisive, but not authoritarian. He would have said: "Very well, then; you are likely to die without surgery, in my opinion. I cannot be 'responsible' for you. I urge you to seek other competent advice, but the decision is yours."

The last word on the subject had neither been said at the luncheon table, nor has

it been written here. The generality is established that the doctor's leadership can be used, like any other of his tools, for healing or hurt, depending primarily upon his individual skill and judgment. And the conversation has further indicated some subtleties which could justify the attention of almost any doctor. Can he recognize when his relationship to the patient has become more authoritarian than he himself thinks it should be? Can he recognize the reasons in him, or in the patient, why it became so? And does he know what to do about it?

SEQUEL

THE DISSATISFIED PATIENT

A doctor may have a too-authoritarian relationship and yet remain comfortably unaware of its existence. Neither he nor the patient feels like complaining. If, on the other hand, the patient is ignoring the doctor's "authority," or attempting to give orders to the doctor, both the patient and the doctor are unhappy. Dr. Dickson, at a later luncheon conversation, told me of such a patient, who finally, in a huff, signed herself out of the hospital. If the patient thus chooses to terminate the relationship, to "fire" the doctor, there is, of course, little we can do; but should the doctor ever terminate it? Should he resign from the case, if the patient is uncooperative, disobedient, dissatisfied and critical? The mere fact that the patient exhibits these traits is additional evidence of rebelliousness toward authority, which is an emotional disorder, for which treatment is desirable. Therefore, if the doctor withdraws from the case, for whatever reasons, he may be doing the patient psychological harm by missing a treatment opportunity.

Of course, no one enjoys criticism; but if a doctor reacts over-emotionally to a patient's criticism, it may be, so Dr. Dickson suggested, because he felt "threatened" thereby. This term is used in its psychological sense — a danger to one's self-esteem, which (according to the Sullivanian school of psychiatric theory) causes anxiety, which then may be converted into anger and other emotions; and these emotions then may cloud the doctor's judgment.

However, before we speak of the psychological "threat," we need to remember that there is a realistic threat to the doctor, in the uncooperative patient. He may die, and we may be blamed for it. Under such circumstances, to allege that the deceased was uncooperative is not only a feeble defense, but also in poor taste. One does not speak ill of the dead. Since in my work as a psychiatrist, I seldom am "responsible for" patients in danger of dying — they risk their comfort, not their lives, in disobeying me — I decided to ask Dr. F. Janney Smith for his opinions. He said that the problem seldom comes up, in a severe form. The patient's minor deviations from the recommended program are a matter for discussion and repetition of the advice, but not for terminating the relationship. However, if there were extremely flagrant deviations from his advice, seriously endangering life, he agreed that it would be necessary, in one way or another, to disclaim "responsibility" for the patient. If one cannot protect the patient, he must protect himself. Relatives expect us, quite illogically, to "make" the patient do what he should. If he is in serious danger through his disobedience, we are obligated to use every means at our disposal — including the "rejection" of the patient, objectionable as it may be psychologically — to influence him.

Such situations being rare, we can return to the idea that the doctor who is overly angered at his patient's foibles feels that way because of being psychologically "threatened." In medicine we have no clear-cut, objective measure of whether or not we are doing a good job. If the motor runs smoothly, the mechanic has proved himself; but if the patient gets sicker, this is no proof of the doctor's lack of competence. We should not be judged entirely by our results; and the esteem or disesteem in which our patients hold us is a highly inaccurate standard. We must, by and large, judge ourselves. Dr. Dickson summed it up in the word, "confidence." The doctor knows, by constant comparison of his work with that of other physicians, what his capabilities are, and becomes secure in his feeling of confidence in himself. His self-esteem is then not damaged by the patient; he does not become emotionally upset, nor does he need to defend himself by arguing with the patient, or by dismissing him.

I objected to the word "confidence," and offered instead a word that, at first glance, seems to be just the opposite — "humility." The thought is that, in a given instance, my best may not have been as good as some other doctor, hypothetically, could have done, but it was the best I could do. Of course, by "confidence," Dr. Dickson does not mean to imply conceit, "I never make a mistake;" and by "humility," I do not mean to imply uncertainty and doubt, a feeling that he made a mistake just because the patient alleges it. Probably Dr. Dickson and I are saying the same thing; and our next luncheon conversation may be on semantics rather than medicine. He is stressing the absolute necessity that the doctor know his business, and know that he knows it; and I am stressing the need to listen tolerantly to a point of view which you "know" is incorrect. Since you don't know everything, it is always possible that even the uneducated can teach you some small point; and even if he teaches you nothing, you may understand better why he thinks as he does. Understanding why people think incorrectly is psychotherapy.

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ANOMALOUS RETINAL CORRESPONDENCE: DIAGNOSTIC TESTS AND THERAPY*

JOSEPHINE S. KUKORA**

The subject of anomalous retinal correspondence has been presented by others, and it still remains an important factor in attempting to establish a cure in strabismic patients. It has been our experience to find a large number of patients with anomalous retinal correspondence who achieve normal correspondence with preoperative treatment, also a few with persistent anomalies of sensory adaptation postoperatively, who may or may not develop normal correspondence by orthoptic therapy.

Let us attempt to define normal retinal correspondence before going into the abnormal type of retinal correspondence:

Normal correspondence exists when two images falling on corresponding points of the two retinas have a common visual direction. Normal correspondence is an indication of normal sensory localization of images despite a motor anomaly.

The age of the patient and his adaptability, as well as the intensity and duration of the anomaly are to be considered in desiring a cure. Fusion with normal retinal correspondence and vergence control are indicative of postoperative binocularity of vision[1].

Anomalous retinal correspondence is manifested in two ways: (1) Localization in two different directions of stimuli received normally by corresponding elements, as the two foveas, and (2) localization in the same direction of stimuli received normally by non-corresponding retinal elements, as the fovea of the fixing eye and an extrafoveal area of the retina of the deviating eye.

In a normal situation the images perceived are falling on two foveas, so that fusion results. In strabismus, the image is received on the fovea of the fixing eye, but on a disparate or more peripheral point of the squinting eye. It is impossible to fuse, so the result is diplopia. Diplopia is undesired so suppression at the fovea results, and the next step is the development of anomalous retinal correspondence.

So anomalous correspondence becomes a means of adjustment or perhaps a close second to fusion. There must be some past expereince in binocular vision; otherwise diplopia could not be aroused.

Anomalous retinal correspondence is present in a high percentage of children with heterotropias developing early in infancy. It is less common in tropias becoming manifest after 3 years of age or in small angle deviations, say, 15 degrees or less.

Anomalous correspondence may exist in various conditions. It may be present when the usually dominant eye is fixing but absent when the other eye is forced to fix. In divergent strabismus with one eye fixing and the other divergent, it may be

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**Chief Orthoptist, Department of Ophthalmology.

present, but with binocular fixation a normal retinal relationship may exist.[2]

Anomalous retinal correspondence is stimulated and strengthened by use and becomes unstable without use, indicating a need for monocular occlusion.

There are certain contraindications for preoperative orthoptics which we can mention here:

1. Those patients with large deviations, 20° or more.
2. Young patients in whom anomalous correspondence has not become established, as those with recent onset of squint.
3. Adults where cosmetic correction only is desired.

In a subject with normal retinal correspondence, the use of corresponding elements means single vision and the use of disparate elements creates double vision or diplopia. Anomalous retinal correspondence is said to exist in a person when elements of the two retinae which are disparate, such as the fovea of one eye and an extrafoveal area of the other eye, have a common visual direction. A patient with anomalous correspondence will see double when fixing with both foveas with the visual axes parellel, and single with the fovea of the fixing eye and an eccentric element of the other eye. This can be demonstrated by the amblyoscope. At the objective angle (the patient's angle of deviation, where any redress movement is no longer present), the patient will see double without being able to superimpose the targets presented to each fovea. However, at a lesser angle the patient may see a single superimposed picture of the two targets presented, using the fovea of one eye and an eccentric retinal area of the other eye. A comparison of the objective angle or relative position of the eyes, is made with the subjective or localizing angle, to measure the angle of anomaly.

In examining for diagnosis, in a case of concomitant strabismus the patient can be made aware of diplopia if the two fields are differentiated as by a colored filter. If the colored filter is placed in front of one eye while the patient is fixating a small light, the patient will see double — one colored and one white light. In an esotropia the displacement will be homonymous, and in exotropia, crossed, provided retinal correspondence is normal. Vertical displacement can be seen in accordance with any vertical anomaly; the amount of displacement should coincide with the deviation.

In a patient with anomalous correspondence, the localization will not agree with the position of the eyes. The subjective angle will be smaller than the objective, and the images may even be superimposed at zero; or the localization may be completely opposite, as for example, a patient with esotropia may show crossed diplopia, and a patient with exotropia may have uncrossed diplopia.

If the objective angle (motor anomaly) and the subjective angle (sensory anomaly) are equal, the patient is said to have harmonious abnormal correspondence. If the subjective angle is less than the objective, the patient is said to have unharmonious abnormal retinal correspondence. If there is crossed localization instead of uncrossed or vice versa, the diplopia is termed paradoxical.

On the amblyoscope the same conditions may be found. The arms of the instrument can be set at the patient's objective angle of squint. If the patient superimposes the targets at his objective angle, he has normal retinal correspondence. If he superimposes

at a lesser angle, he has abnormal retinal correspondence. The abnormal correspondence is said to be harmonious if the subjective angle is zero, and unharmonious if less than zero.

The state of retinal correspondence can be determined by the so-called after-image test. In this test, first one retina is exposed to a horizontally placed lighted filament. The bulb has a band or ring which bears a fixing dot and which conceals the filament. The patient is asked to fix on the dot for about ten seconds with one eye at a time: The tubular bulb is horizontal while one eye fixes and vertical while the other eye fixes, with the non-fixing eye always covered. After the exposures the patient will perceive an after-image of two straight lines with a hole or gap in the middle. The position of the lines will determine the visual directions of the foveas. If the lines coincide to form a cross, and the two dots coincide, the patient has normal correspondence. If the dots are displaced to the right or left, the patient has anomalous correspondence. The after-image test is an indication of the sensory relationship between the two eyes. A positive after-image suggests a deep-seated anomalous retinal correspondence and tends to suggest a poor prognosis.

Treatment of abnormal retinal correspondence is usually in three steps:

1. Occlusion
2. Major amblyoscope
3. Physiologic diplopia

Abnormal correspondence is a binocular condition with disparate retinal elements receiving the impression of a single object or image viewed. The fixating eye uses the fovea and has no suppression, but the squinting eye uses a more peripheral element and has suppression between the periphery and the fovea. Now, if fixation is switched, so is the suppression area.

The logical step is to occlude one eye constantly. It must be borne in mind that the angle of squint is not changed; that is, no motor change results, but the sensory pattern will be altered.

Occlusion is alternated if alternation is present or if amblyopia is absent. If amblyopia is present, naturally the better eye only is occluded until the vision becomes equal in the two eyes or within two lines of the Snellen chart. In this way as vision improves, the sensory pattern can be altered. Age and work have to be considered for psychological reasons. As soon as vision has improved, then the major amblyscope can be used under the technician's supervision only.

The methods we use on the amblyoscope, and we use a Lyle Mapor as well as the Troposcope, are alternate flashing at the patient's objective angle of squint, oscillating the instrument arms, and using the monocular diplopia routine (Walraven Technique). The arms of the ambiyoscope are set at the patient's objective angle of squint. We start with larger targets and work to foveal sized targets. The lights are flashed alternately from one eye to the other. We increase the light intensity in front of the habitually non-fixing eye. The corneal reflexes are watched closely, as stimulus to accommodate may change the convergence angle and foveal fixation may be lost. The foveas thus are constantly being stimulated by light. Some of the instruments have

automatic flashing devices. I prefer to flash manually, since there is less chance of losing sight of corneal reflexes. The arms of the instruments are locked at the angle of squint, and a large side to side sweep is made within the angle of squint, watching again the corneal reflexes for any change due to accommodative effort. In addition, we have the patient fix with the fovea of the habitually squinting eye on a test target of foveal size while the other slide, a larger size, is gently moved over the other eye in an angle of about 20 degrees. This is quite often referred to as "massaging the macula". The side which is oscillating or "massaging," constantly invades the suppressing area in the anomalous region. The suppression area becomes smaller, and the targets seem to be moving closer to each other; then the arc of movement is reduced. When the patient is able to superimpose at his objective angle, the excursion is continued with alternate flashing again, until the pictures can be held fused for at least a count of fifty. This is then followed by some amplitude training: holding fused images while symmetrical convergence and divergence is exercised. The technician utilizes the method which she feels is most suitable for the particular patient at hand. Some patient's respond favorably in a short time, others take a longer time. We feel that after six or even ten sessions (rarely more than six), and after amblyopia has improved, surgery is indicated. Then we resume postoperative therapy, if indicated, the same as preoperative.[3]

The procedures for treatment as here mentioned are not necessarily applicable to all patients with anomalous retinal correspondence. There are certain patients who, despite almost perfect alignment of visual axes by surgery, never gain a clear bifoveal fixing pattern. They eventually start suppressing again and do not have binocular vision although preoperative treatment was given.

Patients must be "picked" for therapy. Age, attention-giving ability, and attendance in the office are to be considered. Cooperation from, and understanding of parents as to what is desired is essential in selection of patients for therapy. When a child is brought into the office for treatment of crossed eyes, and we institute exercise, patching, and glasses before surgery, parents must have some knowledge of what we are doing and why. Then, after surgery, again the parents may question and rightfully so, the effects of prolonged treatment. The orthoptist must be prepared to inform them and reasonably answer their queries. In this role, the orthoptist must realize her limitations, and not assume the responsibilities of the ophthalmologist.

SUMMARY

In strabismus, normal retinal correspondence represents bifoveal fixation at the objective angle of squit. Abnormal retinal correspondence represents a perverted sensory adaptation to a motor anomaly.

Diagnostic tests of dissociation by colored filters, after-image test, and major amblyoscope are described.

Treatment by occlusion, amblyoscope and diplopia are described.

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OCCULT CYSTIC FIBROSIS*

GORDON MANSON, M.D.**

Since 1938,[1] when Andersen differentiated cystic fibrosis and coeliac disease as separate pathological entities, cystic fibrosis has been considered as an 'all or none' disease phenomenon. It was usually thought that an affected child in whom the diagnosis could be proven was unlikely to survive many years and that his remaining years would be punctuated by intercurrent respiratory infections, steatorrhea and subsequent malnutrition. It has since become apparent that the disease is a generalized process which may make its appearance in the form of chronic pulmonary infection, a malabsorption syndrome characterized by steatorrhea, foul stools and malnutrition or as meconium ileus in the newborn period.[2] In 1952, Bodian[3] reported extensive liver involvement characterized pathologically by biliary cirrhosis and biliary concretions. In 1953, Di Sant'Agnese[4] and his group demonstrated that sweat electrolyte concentrations were significantly increased in these patients and that this determination had diagnostic value, especially as a screening test, inasmuch as it could be readily done without the insult of duodenal drainage. Webster and Williams[5] then reported mild disturbances of liver function, Gatzimos and Jowitt[6] found cystic fibrosis a cause of neonatal jaundice and in 1954, Di Sant'Agnese[7,8] reported patients with the disease who showed marked disturbance of liver function. It is now clear that, despite the inadequacy of the term 'cystic fibrosis', the disease is one which often involves many organs and from which a variety of symptoms may arise. Schwachman[9] and Di Sant'Agnese[7] have both suggested the concept of 'partial fibrocystic disease' and Schwachman[10] has emphasized the occurrence of dissociation of enzyme activity in pancreatic secretions in these patients. It was further shown that an individual with partial cystic fibrosis and minimal enzyme deficiency might be followed for a number of years and then observed to develop the total disease picture. In 1955, McGrady and Bessman[11] studied electrolyte concentrations of saliva in cystic fibrosis patients and found them elevated in much the same way as sweat electrolytes and proposed this method as a screening test for the disease. Our experience at this hospital, has indicated that in our hands, measurement of sweat electrolytes obtained by the collection methods of Shwachman[2] or Barbero[12] is very satisfactory while the collection of suitable samples of saliva from young subjects is fraught with considerable error. It is now generally accepted that, if certain few other diagnostic considerations can be reasonably excluded, sweat chloride concentrations in excess of 60 meq./1. require that cystic fibrosis be ruled out.[13]

Since 1938, then, three basic concepts have arisen regarding cystic fibrosis: first, that it is a generalized disease involving many organs; secondly, that it has a wide spectrum of severity, ranging from barely perceptable secretory dysfunction in several glands to acute intestinal obstruction in the newborn period or suffocating respiratory insufficiency in later childhood; and thirdly, that it is usually a progressive disease though many years may elapse before the patient is much disabled by it.[14,15,16]

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*This terminology is used with reservation. Schwachman[2] enumerates six synonyms for the disease. Presently there is no generally accepted term for the disease. Cystic and fibrotic changes are seen but the basic biochemical defect has so far eluded definition. Cystic fibrosis now seems to at least have the approval of popular usage with the recent formation of the Cystic Fibrosis Foundation.

**Associate, Department of Pediatrics.

Recently we have had the opportunity to study three patients whose cystic fibrosis has been strikingly characterized by minimal symptomatology and excellent growth and nutrition. The very mild nature of their disease prompted a review of the literature and it was found that few similar patients are reported. For this reason the present cases are reported.

CASE 1. This 13 year old white female was admitted for the investigation of a chronic productive cough of ten years duration. It began with an episode of bronchopneumonia at three years of age and had persisted to the present without progression of severity. Cough was worse on rising in the morning and before bedtime. Occasionally it was productive of yellow sputum but there was no seasonal pattern to the cough. At five years of age, the patient was hospitalized twice for investigation of the cough. On one admission, she underwent adenotonsillectomy and, on the second, nasal polypectomy. Three years before admission to this hospital, she was admitted to a second hospital where extensive studies were carried out and the girl started on a program of bacterial vaccine therapy. Since that time, she had been given extensive antibiotic therapy and hyposensitization without relief. In the year before admission to this hospital, she had lost two months of school attendance because of her chronic cough. Menarche occurred in December, 1955 and menstruation since had been uneventful. Family history revealed no allergy or pulmonary disease.

Physical examination revealed a splendidly nourished, mature, thirteen year old girl who fell in the 50th percentile in reference to weight and the 75th percentile in reference to height on the Iowa Growth Curves. A few, scattered, medium rales were heard in the RML and in the upper part of RUL. Similar, but less marked, findings were noted in the LLL. The liver edge was felt 1 cm. below the right costal margin and the tip of the spleen 2cm. below the left costal margin. Slight clubbing and cyanosis of the digits and toes was apparent, being less marked in the latter.

Hemogram and urinalysis were normal. Total eosinophile count was 32 per cu. mm. Sedimentation rate (Wintrobe) was 1 mm./hr. L.E. test was negative. Sputum culture showed no growth of fungus but abundant growth of Staphylococcus aureus and Pseudomonas aeruginosa. Total serum bilirubin was 0.33 mg. per cent. Serum cholesterol was 230 mg. per cent, 42% of which was ester fraction. Bromsulphalein test showed 2% retention at 45 minutes and none at 60 minutes. Total serum proteins were 7.2 gm. per cent, 4.3 per cent of which was albumin. Alkaline phosphatase was 7.2 Bodansky units. Glucose tolerance curve was normal. Cephalin-cholesterol flocculation test showed 2-plus reaction. Thymol turbidity test was reported as 4 units, the thymol flocculation test showed 2-plus reaction. Tests for tryptic activity in the stool on three successive days showed tryptic activity to a dilution of 1.425. Stool specimens gave a 2-plus reaction for fat when stained with Sudan III. Serum carotene was 50 micrograms per cent. Serum vitamin A level was 16 micrograms per cent. Sweat chloride determinations on samples collected by the patch method of Shwachman yielded values of 164 and 210 meq./1. Similar determination on the patient's father gave a value of 70 meq./1. Her mother was dead. Duodenal drainage was done, the position of the tube checked fluoroscopically and the following results obtained: trypsin 3.8% of normal activity, amylase 6%, lipse 3%. The ph was 5.0 and the viscosity 12.7. A second drainage was done and these results confirmed.

The patient's chest films are shown in Fig. 1. Films of the paranasal sinuses showed definite haziness of the maxillary sinuses without thickening of the mucosa.

Figure 1: Heart and aorta are normal. There is an extensive infiltration throughout both lungs from apices to bases. Hilar nodes are prominent and some calcified nodules are seen.

During her hospital course, the patient was placed on oxytetracyclene in large doses, iodides, antihistaminics and was given frequent postural drainage. Local therapy was directed towards improving drainage of paranasal sinuses. At the time of discharge, the patient had improved slightly as far as her cough was concerned. She has been followed in the Out-Patient Department and has since been placed on Pancreatin tablets. She has also been provided with Alevaire aerosol equipment for home use. Some improvement of her chronic cough has been obtained with aerosol treatment.

CASE 2. This 7 year old white female was admitted for investigation principally because of the proven existence of cystic fibrosis in a younger sibling. At 6 weeks of age, diagnosis of the disease was suspected in the patient on the basis of a negative test for tryptic activity on one stool. This was not pursued further, however. At 3 years of age, the patient developed a chronic productive cough of mild degree. By 6 years of age, the patient began to be treated periodically with Alevaire-Isuprel aerosols

and iodides for occasional episodes of productive cough without significant fever or illness. Parents noted that iodides afforded especial relief. While stools had not been observed by the parents to be particularly abnormal, except for their bulk, they were noted to be less bulky and odorous after Viokase (4x USP Pancreatin) ½ tsp. three times daily was begun a year before admission. Appetite, though good, was never excessive.

Family history was of particular interest and is shown diagramatically in Fig. 2,** together with sweat chloride determinations on surviving members.

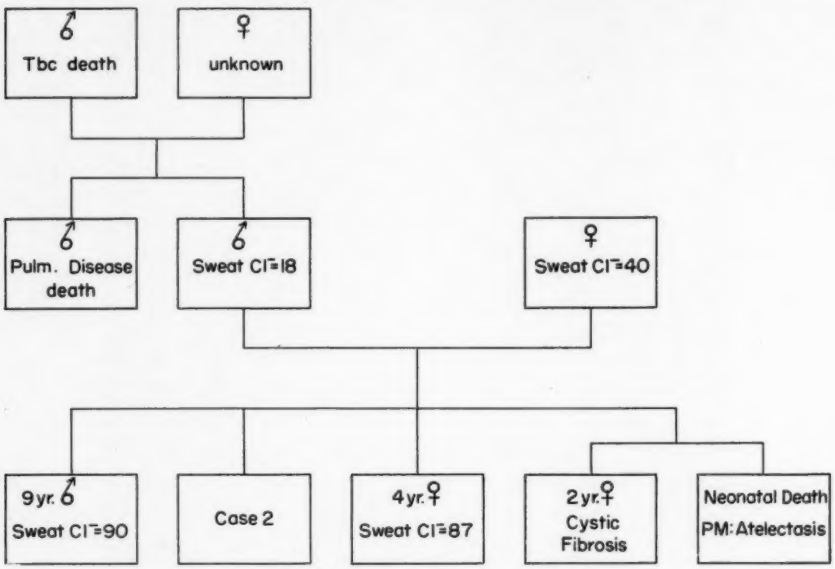

Figure 2. Family history, case 2.

Physical examination revealed a pleasant, healthy appearing girl in an excellent state of nutrition. Her height and weight were found to be median for her age when plotted on the Iowa Growth Curves. There were no physical abnormalities.

Hemogram and urinalysis were normal. Total serum bilirubin was 0.5 mg. per cent. Alkaline phosphatase was 5.2 Bodansky units. Total serum protein was 7.0 gms. per cent, 5.0 gms. per cent of which was albumin. Prothrombin activity was 70% of control. Cephalin-cholesterol and thymol flocculation tests showed no reaction. Thymol turbidity test was reported as 1 unit. Glucose tolerance curve was normal for three hours. Tests for tryptic activity on stools for three successive days showed no reaction. Stool specimens gave a 3-plus reaction for fat when stained with Sudan III. 3-plus starch was also found in these specimens. Serum carotene was 15 micrograms percent and the serum vitamin A level 3 micrograms percent. Sweat chloride using the collection method of Barbero et al. was 120 meq./1. and with the patch collection

**Sweat chloride levels on the family of case 2 were obtained by R. G. Cornell, M.D. as part of a study supported by a research grant from the Henry Ford Hospital.

method of Shwachman was 97 meq./1. Duodenal drainage was done three times, the position of the tube checked by fluoroscope and no activity of trypsin, lipase or amylase was demonstrated in the secretions. The pH was 3.6 and the viscosity 1.79. Sputum culture grew only the normal respiratory tract flora on several specimens, without any dominant organism.

Chest films revealed no abnormalities.

The girl's hospital course was uneventful and she was discharged following studies reported above on Viokase ½ tsp. three times daily. Previously employed aerosol treatment was to be used as necessary for any episodes of respiratory symptoms during which the use of liberal doses of tetracyclenes was suggested. The patient was referred to her local physician for further care.

CASE 3. This 5 year old white male had been followed in this clinic since the age of three months. His earlier years were quite uneventful except for an episode of salmonellosis which was successfully treated at 3 months of age and adenotonsillectomy performed 2 years before the present admission. At a pre-school examination the child was described by the examiner as being "in excellent condition".

Present illness began 2 months before admission rather suddenly with the onset of 4-5 bowel movements daily and associated fever and vomiting. This episode lasted 3 days and since that time the boy had passed 4-5 somewhat loose stools daily. Three days before admission, the stools became watery and foul smelling, constant frequent loose stools were passed day and night and, on two occasions, a little fresh blood was observed in the stool.

Physical examination revealed a well nourished boy without physical abnormalities other than moderately hyperactive bowel sounds. When plotted on the Iowa Growth Curves, he was found to fall in the 50th percentile in reference to height and in the 50th percentile in reference to weight. The impression of the admitting physician was 'possible chronic ulcerative colitis'.

Upper gastrointestinal studies and small bowel studies showed no abnormalities. The barium enema was normal. Chest films revealed no abnormal findings. Sigmoidoscopy to a depth of 23 cm. showed no abnormalities.

The hemogram and urinalysis were normal. The sedimentation rate (Wintrobe) was 1 mm./hr. Agglutinations for typhoid and paratyphoid were negative. Stool culture grew a normal gastrointestinal flora. Two determinations of sweat chloride concentration by the patch method were 127 meq./1. and 214 meq./1. Two successive stool specimens showed tryptic activity to a dilution of 1:425. No evidence of ova or parasites was found in the stool. Duodenal drainage was done and tryptic activity was found to be 23% of normal, lipase 26% and amylase 34%. Viscosity was 2.21 at 4° C. Unfortunately, pH was not determined. Liver function studies were not obtained on this admission.

During his hospital course, no abnormility of bowel habit was noted. The child was completely asymptomatic. He was discharged and presently remains on a 20% protein diet, an aqueous multiple vitamin preparation containing 1000 I.U. vitamin D

and 100 mg. vitamin C plus added B-complex, Pancreatin granules 1 teaspoon three times daily and penicillin G tablets once daily. His subsequent course is being followed in the Pediatric Clinic.

DISCUSSION

In Case 1, remarkably slow progression of chronic pulmonary disease is seen and it was to the tracheobronchial tree that the patient's only symptoms were referred. In former years, she had been seen in two excellent clinics where the diagnosis of cystic fibrosis was not considered at the time when the sweat chloride determination was not available as a screening test. Our attention was directed towards this diagnosis by the patient's high sweat chloride. At the time she presented for study, this patient showed definite signs of chronic lung disease in the form of mild clubbing and cyanosis of the distal extremities. In view of these irreversable changes, the prognosis regarding this girl's pulmonary status is necessarily guarded. This patient, however, clearly indicates the necessity of including sweat chloride determinations in the study of any child or young adult who presents with symptoms suggesting chronic pulmonary infection. Where these are abnormal, duodenal drainage and assay of the secretions is indicated. It should be remembered that patients with fibrocystic disease may have acid duodenal secretions[2] and where these are found, the position of the tube should be checked fluoroscopically to assure the validity of the test.

It is likely that Case 2 might have gone unrecognized for some time except for the occurence of frank cystic fibrosis in a younger sibling. This girl is the most unusual patient with the disease we have seen in this clinic, being characterized by excellent growth, nutrition and a completely normal physical examination. Her family tree is remarkable in that the frequency of afflicted siblings exceed the previously reported 1 to 4 ratio[3]. A geneology showing this same feature has been reported previously from this department[17]. Certainly these and other similar observations demonstrate that the disease does not follow the simple pattern of a Mendelian recessive. Two of the patient's surviving siblings, excluding the sibling known to be affected and under treatment, have been shown to have abnormal sweat chlorides and we hope to be able to study these children in the near future. Whether the magnitude of sweat chloride elevation is an index of gene expressivity is presently under study. We have no clear idea what this girl's subsequent course is likely to be, recorded experience being lacking in such mild cases. One's only recourse is to the observation that cystic fibrosis is a progressive disease. It would be speculation to suggest that by age 12 years, Case 2 might resemble the current status of Case 1.

In Case 3, the possibility of cystic fibrosis was raised by an abnormal sweat chloride obtained as a part of study for an unexplained diarrhea. Duodenal drainage was corroborative, though only partial pancreatic insufficiency was demonstrated. The boy has derived complete control of symptoms from replacement therapy with pancreatin and is now completely asymptomatic. In the absence of chronic pulmonary infection, this situation will probably continue. However, in patients with chronic pulmonary infection, despite complete enzyme replacement therapy, malabsorption secondary to chronic infection eventually precludes adequate nutrition. Usually, such infection is caused by staphylococci and the development of resistant strains is soon seen with all the attendant problems in treatment they create. For the present, this

patient is doing splendidly but his subsequent course must remain a matter of conjecture.

The occurence of such minimal cases of cystic fibrosis as these necessitates revising our thinking regarding the extent of the full spectrum of the disease. Some years elapsed before it was demonstrated that chronic lung disease, meconium ileus, steatorrhea, heat stroke and cirrhosis could all arise from the same generalized disease. It is likely that much further observation will be necessary before the incidence of occult cystic fibrosis in adults, presently only sporadically recognized, can be ascertained.

SUMMARY

1. Three cases of occult cystic fibrosis are reported.
2. The role of the sweat chloride determination as a screening test in the patient with chronic pulmonary infection or unexplained stool abnormalities is emphasized.
3. A geneology suggesting transmission of the disease other than as a Mendelian recessive trait is reported.

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OXYGEN PHYSIOLOGY, NORMAL AND ABNORMAL

The Fifth Edsel B. Ford Lecture, 1956

DONALD D. VAN SLYKE, Ph.D.*

Oxygen physiology began in the 18th century with the discovery of oxygen and its necessity for the life of animals by Priestley in England and Lavoisier in France. The modern development of the field may be said to begin in the 1890's with the work on blood gases of Christian Bohr and August Krogh in Denmark and J. S. Haldane in England, where Douglas and Barcroft shortly after joined in an epoch of basic contributions. American work in the field was stimulated by Christen Lundsgaard who brought the lore of the Danish school when he came to the Rockefeller Institute for an active period of seven years beginning in 1917. Lundsgaard's demand for a rapid and accurate blood oxygen method was responsible for adapting the old Van Slyke "volumetric" CO_2 apparatus to oxygen determination, from which the present manometric method derived. Lundsgaard's studies of blood oxygen unsaturation in cyanosis and circulatory conditions led in the Rockefeller Hospital to Stadie's initiation of the arterial puncture and the practical application of oxygen therapy. Knowledge of blood oxygen in circulatory conditions has been brilliantly expanded in the past decade by the school of Cournand, Richards and Riley for the general circulation, and of Schmidt and Kety for the brain.

Anoxia. Haldane's early work showed that the brain is especially dependent on a continual supply of oxygen to maintain, not only normal function, but organic existence. As shown by Kety, the adult human brain normally uses about 45 ml. of oxygen per minute. If the brain's oxygen consumption is cut down by 10 per cent one begins to get the first mental signs, a little difficulty in concentrating thought. If the consumption is cut down by 20 per cent there is emotional instability and confusion. As Haldane observed, the effects are identical with those of alcoholic intoxication. If oxygen consumption is cut down by 40 per cent coma ensues. If the brain's blood supply is completely cut off, as by a cuff around the neck, unconsciousness follows in a few seconds, and irreversible damage after for or five minutes. Haldane's statement: "Lack of oxygen not only stops the engine, it wrecks the machinery," has become classic. Cerebral anoxia can be particularly dangerous because it can come on without subjective discomfort. A sudden rise to high altitude, or inspiration of air containing carbon monoxide, causes first disorientation, then loss of consciousness, without warning signs of distress.

Anoxia of degree less than that which causes serious immediate effects can have effects that are cumulative with duration of the anoxia, and may even increase after the anoxia has been relieved, affecting not only the brain, but the heart, the kidneys, and the capillaries. Fatal shock has been observed developing in aviators after their return to normal atmosphere.

Next to the brain, the kidneys appear to be the organs most likely to suffer cellular damage from anoxia. Renal ischemia such as is caused by a few hours of shock from

*Assistant Director, Brookhaven National Laboratory, Upton, New York.

decreased circulating blood volume can damage the tubular cells, casusing renal failure which may require weeks for recovery, or may progress to a fatal result.

Circulatory Adjustments and Oxygen Supply. From the work of the schools of Cournand, Kety, and Homer Smith, and others, one may take 5.3 liters per minute as the approximate average output of the adult human heart at rest, 0.7 liter going to the brain, 1.1 liter to the kidneys, and 3.5 liters to the other tissues. With activity the blood supply to the muscles, skin, and viscera can change greatly; e.g. work can multiply many times the blood flow through the muscles, and Barcroft reported a 50-fold increase in the blood flow of the arm caused by heat. Conversely the muscles and skin can tolerate reduced blood flow for some time. But the brain and kidneys appear to require, and under nearly all conditions of normal body activity, to receive a nearly constant supply of blood and oxygen. It is the task of the lungs and circulation to supply to the working muscles, the active gastrointestinal system, to the skin under conditions requiring accelerated heat removal, the increased supplies of blood and oxygen demanded by these organs, and at the same time maintain the regular supply to the brain and kidneys. Under stress the oxygen requirements of the other organs are met partly by increasing the output of the heart, partly by increasing the proportion of oxygen extracted from the blood that perfuses them. When the heart is weakened the increase in its output is limited, and the amount of activity that can be tolerated is diminished. If the demands of the muscles for work, or of the skin for heat removal, become imperious, the supply to the brain may be in part surrendered, with the results of cerebral anoxia. This can even occur in a normal man forced to great physical exertion on a hot, humid day, with resultant "heat exhaustion," the cerebral effects of which may go as far as coma. If the heart is weakened by disease or age, the tolerance to exertion or heat is decreased.

Types of Anoxia. Barcroft in 1932 divided anoxias into four different types according to their causes. With slight modification this classification holds today: (1) *Arterial anoxia,* in which the oxygen saturation of the arterial blood falls below the normal 98 per cent, because the oxygen concentration in the air breathed is low, or mechanical conditions in the lungs prevent free access of air to the blood, or a right-to-left shunt of blood in the heart-lung area mixes venous with arterial blood. (2) *Anemic anoxia,* caused by a lack of hemoglobin to carry oxygen, or a loss of ability to carry it, as in carbon monoxide poisoning or methemoglobinemia. (3) *Stagnant anoxia,* in which the rate of blood flow through the tissues is slowed, as in decompensated heart failure, peripheral arterial disease, or vascular constriction. (4) *Histotoxic anoxia,* in which tissues are poisoned, as by cyanide, so that they cannot use to a normal extent the oxygen that is brought to them. There is evidence that alcohol and some of the other narcotics act thus on the brain tissue. One could add *high requirement anoxia,* in which the metabolic requirement for oxygen is so increased that it cannot be met even by the acceleration provided by normal lungs, heart, and vessels. Such is the condition in the muscles of a sprinter who develops lactic acid acidosis.

In Figure 1, which is developed from a design of Lundsgaard's, are represented some of the relations of arterial and mixed venous blood oxygen and hemoglobin that are encountered in some normal and pathological conditions. In considering them it should be noted that the oxygen tension of the tissues is most nearly indicated by

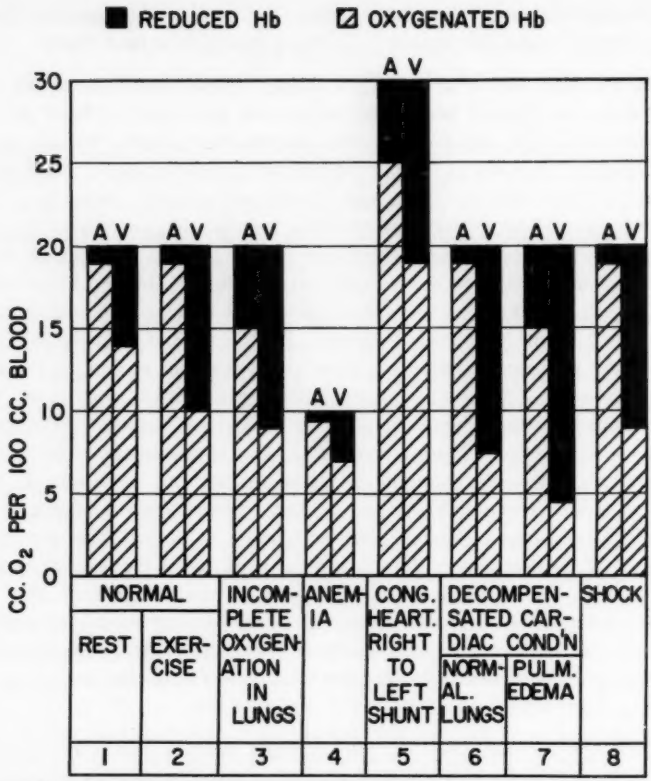


Figure 1. A design of Lundsgaard's representing some relations of arterial and mixed venous blood oxygen, and hemoglobin.

the *oxygen tension of the venous* blood, and that the latter depends on the *proportion* of venous hemoglobin that is oxygenated. When 50 per cent of the hemoglobin is oxygenated, the oxygen tension is approximately 30 millimeters of mercury, and this, in the mixed venous blood, appears to be about the minimum that may be considered within the optimal physiological range. Column 1 shows normal resting conditions, with 98 per cent of the arterial and 70 per cent of the venous blood oxygenated. Column 2 shows the normal effects of exercise. Respiration is so increased that the arterial blood is still 98 per cent oxygenated. The heart output is increased enough so that oxygenation of the venous hemoglobin does not fall below 50 per cent. Column 3 shows a condition of arterial anoxia. When the tissues extract their allowance of oxygen, even at rest the venous hemoglobin becomes half deoxygenated, and there is no margin available for exertion. Column 4 illustrates conditions in anemia. Circulation may be accelerated so that the venous blood remains 70 per cent oxygenated at rest, as in the case illustrated, but if exercise caused extraction of as much oxygen as in column 2, the venous blood would be completely deoxygenated. Only limited exertion is possible. Column 5 indicates conditions that may be met in a congenital heart case, with a shunt from right heart to left. In response to the chronic anoxia a compensatory

polycythemia has developed. In consequence, although a normal 6 volumes per cent of oxygen is extracted from the blood, the venous hemoglobin is still about 70 per cent oxygenated, and the tissues enjoy normal oxygen tension, despite the fact that the amount of reduced hemoglobin present causes cyanosis. (In more severe cases tissue anoxia *is* present.) Colum 6 shows the effects of stagnant anoxia from retarded cardiac output. Column 7 shows the added anoxia that is suffered when pulmonary edema adds arterial anoxia to the stagnant anoxia. The last column shows the effect of shock and retarded circulation on the mixed venous blood. In all the conditions, the degree of the anoxia can vary in the different tissues, and be influenced by changes in the blood flow distribution to different sites. But whenever there is a low oxygen tension in the mixed venous blood, the organism can maintain local oxygen tension, in the brain for example, only at the cost of restriction elsewhere.

Cyanosis. Lundsgaard studied the causes of cyanosis and came to the conclusion that when the mean capillary concentration of reduced hemoglobin, estimated as midway between arterial and venous, exceeds about 5 grams per 100 ml. of blood (an oxygen unsaturation of 6.6 volumes per cent), cyanosis is likely to become apparent. Referring to Figure 1, we can see the significance of this estimate in the conditions exemplified if we take the venous unsaturations as representing blood from the skin. The mean capillary unsaturation value as estimated by Lundsgaard is indicated by the midpoint between the two black columns in each of the eight examples, the distance measured from the top indicating the volumes per cent oxygen unsaturation. In the normal exercising subject it is 5.5 volumes per cent, somewhat short of the cyanotic threshold. In column 3, representing arterial anoxia, the mean unsaturation is 8 volumes per cent, and cyanosis may be expected. In column 4, representing anemia, even complete utilization of the oxygen, with none left in the venous blood, would not produce enough reduced hemoglobin to show as cyanosis. In anemia it is evident that even severest anoxia is not likely to reveal itself by cyanosis. By contrast, in column 5, showing arterial anoxia and polycythemia, there is 8 volumes per cent mean unsaturation, well over the cyanotic level. Nevertheless, because of the great concentration of hemoglobin, the venous blood is 64 per cent oxygenated, and the tissue oxygen tension indicated is such that no embarrassment from low oxygen activity in the cells is to be expected. Such a subject, despite marked cyanosis, may have no symptoms of anoxia, unless the arterial anoxia is greater than in this example. In both of the decompensated cardiac cases mean capillary unsaturation is well into the cyanotic range, the greater being in the case in which pulmonary edema adds arterial anoxia to stagnant anoxia.

Controlled Oxygen Therapy. A year after Lundsgaard came and started his work the 1918 influenza epidemic swept the world. Many cases developed bronchopneumonia. Cyanosis was frequent, and a grave prognostic sign. It was uncertain whether the cyanosis was due to a stagnant anoxia, from decreased heart output, or was due to arterial anoxia, from incomplete oxygenation of the blood in the lungs. Dr. W. C. Stadie had charge of part of the pneumonia patients in the Rockefeller Hospital and decided to apply Lundsgaard's criteria to find the cause of the cyanosis. The only way to know certainly whether the anoxia was arterial was to analyze arterial blood, and the arterial puncture was not at that time a recognized clinical procedure. A technique for it had been demonstrated in 1912 in Germany by Hürter, but had not been applied

by others. Stadie experimented with the technique, proved it safe, and proceeded to use it in the study of his patients. Stadie was an engineer before he went into medicine, and was able to design a chamber that was arranged for regulation of temperature and humidity as well as oxygen. So far as I know, it was the first such oxygen chamber that was used clinically.

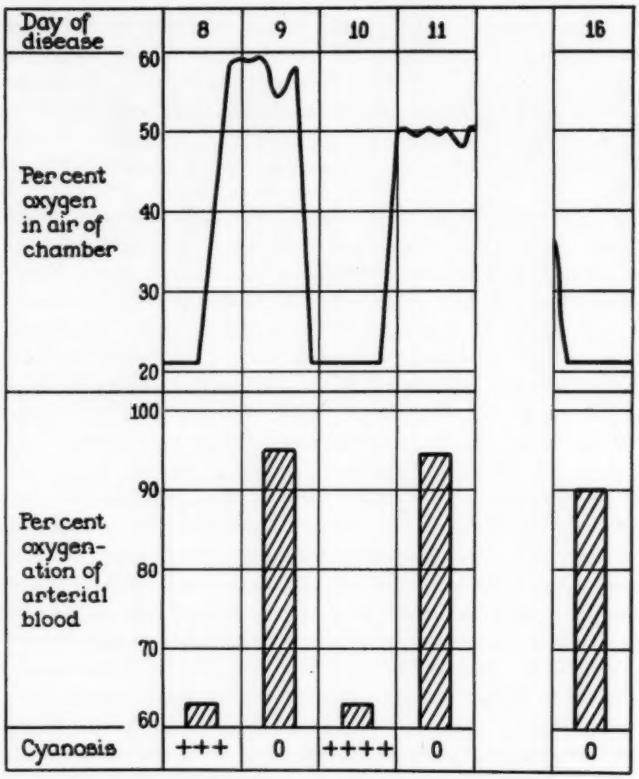


Figure 2. Results with a typical case from Stadie's series.

Figure 2 shows results with a typical case from Stadie's series. It was a patient with intense cyanosis, with a little over 60 per cent arterial oxygenation. When the patient was placed in an atmosphere with 60 per cent of oxygen the arterial saturation went up to 95 per cent. When the patient was returned to ordinary air the arterial unsaturation and the cyanosis returned. On return to the chamber oxygenation was restored and cyanosis disappeared. Eventually the patient recovered. The clinical effects of the oxygen treatment were that delirium disappeared, heart rate went down, respiration became eased. There was no indication that the course of the infection was altered, and Stadie made this clear in his publication, but the stress conditions under which the patient labored were eased. The degree of arterial anoxia that the patient showed in atmospheric air was such as would be caused by an altitude of about 20,000 feet, enough to incapacitate many normal men.

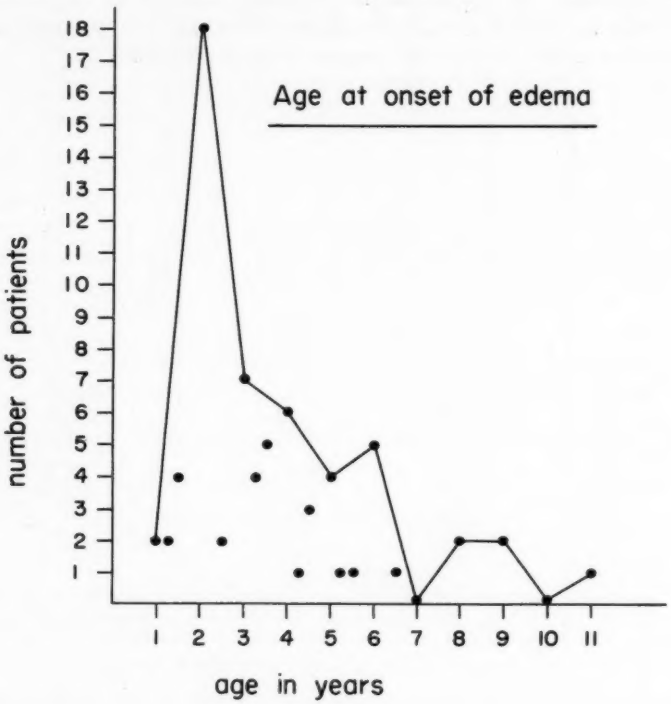
Stadie's work may be fairly said to mark the start of effective systematic oxygen therapy. He laid down the principles of both technique and control. His results were quickly applied in other clinics, and were expanded so rapidly that few of those who now use oxygen therapy as a routine procedure realize the debt that they and their patients owe to Stadie, and, farther back, to Lundsgaard, Haldane, Barcroft, and Bohr.

With the decrease in pneumonia achieved by antibiotics, and with the increased knowledge of blood oxygen in circulatory conditions contributed by Lundsgaard, by Cournand and Richards, Robert Levy, Alvin Barach and others, the application of oxygen therapy has shifted largely to cardiac failure, shock, and other circulatory and pulmonary conditions, the indications and precautions required for oxygen administration have been ascertained, and oxygen administration, more or less adequately controlled by blood oxygen analyses, has become standard procedure.

THE NEPHROTIC SYNDROME

DONOVAN F. HINCHMAN, M.D.*

It is the purpose of this paper to review our 25 years' experience in the treatment of lipoid nephrosis in children. Included in this series are 73 cases that fulfilled the criteria of edema, proteinuria, hypoproteinemia and hyperlipemia. These were all children ranging in age from 12 months to 11 years at the onset of their edema, with no significant hematuria, hypertension or azotemia.



NEPHROTIC PATIENTS ACCORDING TO AGE OF ONSET OF EDEMA

RESULTS

The first five patients received supportive treatment only, including plasma and whole blood transfusions, paracenteses, etc. Three died of intercurrent infection, chiefly pneumococcic peritonitis. Two could not be followed.

The next 30 patients were treated, in addition, with more or less regulated courses of prophylactic antibiotics or sulfonamides. These drugs were also given in therapeutic dosage during acute exacerbations of edema.

*Resident, Department of Pediatrics.

Nephrotic Syndrome

Since 1950, there have been 30 patients treated with the steroid hormones during acute exacerbations of their edema.[13] These have included ACTH, cortisone, hydrocortisone and prednisone. They were routinely given large doses with abrupt cessation of therapy after 10-14 days.[1,7,9,12] Diuresis usually ensued during the administration or shortly after withdrawal of the hormone. Other evidence of remission was usually present; decrease in proteinuria, decrease in serum cholesterol and rise in the serum proteins.[10]

Nitrogen mustards have not been used in the treatment of nephrosis in children at this hospital.[4]

Recently there has been a growing interest in the use of prolonged steroid therapy in nephrosis. Some have suggested that, after an initial course of intensive steroids, hydrocortisone be given 3 consecutive days each week for as long as one year or more.[5,6] Others would use discontinuous therapy only until the urine and serum proteins have been normal for 2-3 months.[8] There are several variations on this same approach. We have attempted this general program on 8 patients. The results of these may be

GROUPS	Total No Cases	Recovered	Dead	Active When Last Seen	Lost	Albumin Only
I Before Antibiotics to 1939	5	0	3	0	2	0
II Before Steroids to 1950	30	11	9	0	8	2
III Steroids for Edema Only	30	9	13	1	6	1
IV Protracted Steroids Therapy	8	1	1	6	0	0
V Hyposensitized	8	6	2	0	0	0

TABLE I

NEPHROSIS STATUS — NOVEMBER, 1956 — 73 CASES

Note: Cases in Group V were also in Groups III and IV.

seen in Table I. We plan to follow the following proposed therapy schedule:[3]

A. Steroid therapy will be instituted as soon as the diagnosis of nephrosis is made (the four cardinal features of edema, proteinuria, hypoproteinemia and hyperlipemia (hypercholesteremia) are demonstrated, with or without hypertension, hematuria or azotemia).

B. *Basic Course of Steroids* will consist of one of the following:

1. Cortisone orally 300-400 mgm. daily for ten days (ACTH will be given on the 9th, 10th and 11th days, in a dosage of 40 units, 30 units and 20 units respectively).

2. Two ten day courses of cortisone (as described in Number 1 above) may be used in certain patients in whom the initial course does not produce cessation or significant diminution of proteinuria. The two courses will be separated by an interval of five days.

3. ACTH 40 units (for patients under two years) to 80 units (for patients over two years of age) in the form of a long-acting preparation given once or twice daily (depending upon the preparation used) for 21 to 28 consecutive days.

C. *Maintenance Steroid Therapy:*

1. Cortisone 300 mgm. orally on each of three consecutive days of each week until the patient is free of proteinuria for two months.

D. *Supplemental Medications:*

1. Antibiotics:
   (a) During intensive steroid therapy while the patient is hospitalized, full therapeutic dosage (10-15 mgm. per pound per day) of oxytetracycline or tetracycline will be given.

   (b) During maintenance steroid therapy, tetracycline or oxytetracycline will be given in a dosage of 5 mgm. per pound per day in two divided doses. If an infection develops in spite of this prophylatic therapy, the amount of antibiotic will be increased to full therapeutic dosage (10-15 mgm. per pound per day) for a minimum of five days and then reduced to the prophylactic dose if the infection has subsided.

2. Potassium salts:
   (a) During intensive steroid therapy and *throughout periods of diuresis,* 3.0 gm. per day of potassium salt (either potassium chloride or a triple mixture of potassium-acetate, bicarbonate and citrate) will be given in three divided doses daily.

   (b) While on maintenance steroid therapy, 2.0 to 3.0 gm. of either potassium salt will be given daily in three divided doses.

3. Calcium salts:
   Calcium lactate is given in a dosage of 4.0 gm. per day in three divided doses as long as patients are on steroid therapy. (Inclusion of cacium salts in the supplementary medications is optional).

E. *Supportive Therapy and Program:*

1. Diet:
   (a) A no-added salt but otherwise general diet is advised. Protein is offered in an amount usual for the patient's age but is not forced.

2. Activity is tolerated, including regular school attendance when the general condition of the patient permits.

3. Plasma Expanders:
   Blood, salt-free concentrated serum albumin or plasma is used when indicated because of intractible edema, or when steroid therapy is contraindicated or whenever it seems feasible to give additional supportive therapy.

4. Abdominal paracentesis will be used in recurrent or complicated cases when abdominal distress becomes extreme.

DISCUSSION

Table I is a summary of our overall results and present status in therapy. Our results, since 1939, have compared favorably with Riley and others.[8,11]

The survival rates in patients treated only with antibiotics and those treated with steroids for edema only are closely parallel. There are indications that those treated with prolonged intermittent cortisone will have a significantly improved survival rate.

It is of interest to note that, in the review of the eight children who were desensitized to bacterial protein, six can be classed as definite cures and only two died. These are too few cases to be of statistical significance but this form of treatment should be investigated further. There were in this series 30% with a definite history of allergy, either in the child or the family. The relatively gratifying results with hyposensitization to the bacterial protein lends support to the hypothesis that childhood lipoid nephrosis may be related to antigen-antibody reaction or to the Schwartzman phenomenon.[2]

SUMMARY

A review is made of the treatment and clinical course of 73 children with the nephrotic syndrome.

Results of treatment with steroids given for edema only have been similar to the use of antibiotics alone.

The use of protracted hormone therapy appears to have promising possibilities. A definite therapy schedule has been set up at this hospital.

Further investigation in the use of hyposensitization to bacterial protein in childhood nephrosis is suggested.

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ONE HUNDRED CASES OF SUBDURAL HEMATOMA FROM 1930 TO 1955 AT THE HENRY FORD HOSPITAL

FRANCISCO GOMEZ, M.D.*

A chronic subdural hematoma is more likely to occur following a minor head trauma than an acute severe head injury. In 1914 Trotter[1] stated that subdural hematoma always had a traumatic origin and emphasized that the head injury was often minor. In the same year he also published his excellent paper in which physiologic peculiarities of the cerebral circulation in subdural hematoma were studied in four different stages. The first, or stage of compensation, is present in the earliest period of the development of this lesion when a certain amount of limited encroachment upon the intracranial cavity can occur without interference with the cerebral circulation. He stated that this was possible because the cerebral spinal fluid found in the area of the hemorrhage could be displaced without producing any effect in function, and because the veins in the same region could undergo a certain amount of compression without restriction of the venous return sufficient to cause congestion.

With the increase in size of the hematoma the second, or stage of venous obstruction, is soon reached. Compression of the veins restricts the venous circulation, causing the veins to collapse. A state of cyanosis in the brain results. The venous congestion produces a characteristic alteration of cerebral function, namely, an increased excitability of the cerebral tissue. This is a local change.

If the hematoma is not evacuated the third, or stage of capillary anemia, follows. This is due to increased pressure in which the remaining blood in the capillaries is squeezed out of the affected part of the brain, which assumes the dead white color of capillary anemia. This is responsible for the subsequent fourth stage of paralysis of function. Thus, paralytic symptoms after a head injury are not always due to actual destruction of the brain substance, and may, in the majority of cases, indicate a compression which has advanced to the stage of capillary anemia.

The great majority of subdural hematomas are located in the lateral aspect of the fronto-parietal region. The size of the hematoma varies from a few centimeters in diameter to cover the complete hemisphere. Its thickness also varies from a few millimeters to four or five centimeters.

Many authors believe that chronic subdural hematomas gradually increase in size. Peet and Kahn[2] stated that repeated bleeding from the highly vascularized outer membrane with rapid increase in the size of the hematoma would best explain the frequent exacerbations and remissions in the symptoms.

Gardner[3] believes that the liquid contents of the hematoma is augmented with cerebrospinal fluid drawn into the cyst by osmotic pressure.

Chronic subdural hematoma is now recognized much more frequently than twenty-five years ago. In 1925 Putman and Cushing[4] found only eleven cases in the records at Peter Bent Brigham Hospital from the previous nine years.

In 1935 Frasier[5] reported six cases from 1932 to 1933 at Union Hospital, Philadelphia. Horrax and Poppen[6] reported eighteen cases in 1937 in a period of two years. Furlow[7] reported sixteen cases in 1936. Kunkel and Dandy[8] reported forty-eight cases in 1939 on the neurosurigical service of the Johns Hopkins Hospital between

*Division of Neurological Surgery.

1914 and 1935. With the introduction of ventriculography in 1918 this condition began to be recognized more frequently and many times was found during the placement of bur holes for ventriculographic purposes.

In our series there has been a definite increase through the years (Fig. 1). From

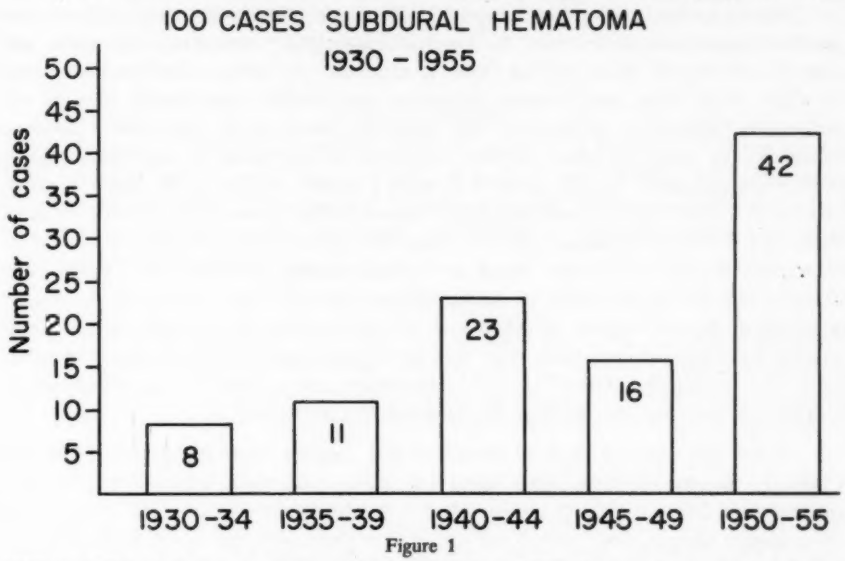


Figure 1

1930 to 1934 eight cases were seen; from 1935 to 1939 the number rose to eleven; from 1940 to 1944 it showed a marked increase and twenty-three cases were seen. For the period 1945 to 1949 the number of cases dropped to sixteen, but, finally, for the last period 1950 to 1955 forty-two cases were seen in this hospital. This apparently marked increase in frequency of occurrence may be due to the greater number of head injuries, but a considerable part of the increase is due to our present knowledge of its etiology and symptoms.

TRAUMA

Since the description in 1857 by Virchow[9] of the condition which he names "pachymeningitis hemorrhagica interna" there has been considerable controversy as to its etiology and pathogenesis. In 1914 Trotter[10] stated that in the formation of subdural hematoma trauma was always present. In 1872 Sperling[11] injected blood into the subdural space of dogs and found that organization began within a week and that the membrane formation was found after three weeks. He carried out similar experiments using defibrinated blood and did not find any membrane, which led him to the conclusion that organization was the result of the fibrin irritating the dura. Microscopically the findings corresponded in all points with those found in pachymeningitis hemorrhagica interna as originally described by Virchow[9].

Similar experiments were made by Spiller[12] in 1899. He nicked the superior longitudinal sinus in cats and dogs sufficiently to produce subdural hemorrhage, and by sacrificing the animals at intervals from six hours to five weeks, was able to study the various steps in the formation of chronic subdural hematoma. His conclusions

were that evidence of new membrane formation was quite distinct after five days, that organization begins near the dura, that after five weeks the membrane is distinctly formed and that subdural hemorrhage may be one of the causes of the formation of a subdural membrane.

Trauma to the head is now accepted as the major etiological factor. Other causes are blood dyscrasias as described by Jones and Knighton[13], metastatic carcinoma, and ruptured aneurysms. As a rule the injury is comparatively mild, in fact, in many cases so slight as to have been entirely forgotten until careful questioning recalled the occurrence. History of trauma is a very important factor in the diagnosis of subdural hematoma, as stated by other authors. However, in our series it was found that in twenty-nine patients it was not possible to elicit a history of head injury, and I certainly agree with Trotter[1] that the role played by trauma in the formation of chronic subdural hematoma is often discounted because of its minor nature. This is especially true in the older patients, who have some degree of cortical atrophy, in whom the cortical veins draining into the sagittal sinus are under tension and any minor trauma in the antero-posterior or postero-anterior direction can very easily tear these vessels at their dural attachment. Bleeding then takes place into the subdural space with subsequent development of a hematoma. Grant[14] in 1935 reported a case caused by the comparatively insignificant force of the breakers encountered in surf bathing.

In the one hundred cases reviewed at this hospital from the period 1930-1955 (Table I) seventy-one cases had a history of trauma. Of these, fifteen (21.1%) were children and fifty-six (78.9%) were adults. Of the fifty-six adults, the younger and older groups were studied. Above the age of fifty there were twenty-six cases (46.4%) and below the age of fifty, thirty cases (53.6%). The youngest of this group with head trauma was two weeks old, and the oldest seventy-six years, with an average age of 37.4 years.

HISTORY OF TRAUMA:		71 cases
ADULTS:		56 or 78.9%
CHILDREN		15 or 21.1%
ADULTS	Above age 50	26 cases or 46.4%
	Below age 50	30 cases or 53.6%
NO HISTORY OF TRAUMA:		29 cases
ADULTS:		26 or 89.6%
CHILDREN		3 or 10.4%
ADULTS	Above age 50	19 cases or 73.0%
	Below age 50	7 cases or 27.0%
THE YOUNGEST OF ALL		2 weeks old.
THE OLDEST OF ALL		76 years.
AVERAGE AGE		42.4 years.

Table I. Trauma in Subdural Hematoma

In the twenty-nine cases with no history of head injury, twenty-six were adults (89.6%) and three children (10.4%). The adults were again subdivided, and above the age of fifty years, nineteen cases (73%) were seen, and below the age of fifty, seven cases (27%). Here we emphasize that in older people who develop subdural hematoma a history of head trauma is not frequently obtained or is so trival that the patient forgets to mention it. The youngest adult was sixteen years old, and the oldest eigthy-two years, with an average age of 56.6 years. The over-all average age was 42.4 years.

RACE AND SEX

In our series ninety-three patients were white and seven colored. Of the ninety-three white patients, seventy-three (78.4%) were male and twenty (21.5%) female. The number of females with subdural hematoma in this hospital is higher compared with other reports such as that of Kunkel and Dandy[8] in which five patients of forty-eight were female (10.4%).

CLASSIFICATION

Our subdural hematomas were classified as acute from zero to forty-eight hours, subacute from two days to two weeks, and chronic with a history of more than two weeks since onset of symptoms or head injury. Of the one hundred cases, seventeen were acute, twenty-eight subacute, and fifty-five chronic. Bilateral subdural hematomas were seen in thirty cases.

SYMPTOMS AND FINDINGS

Unconsciousness after head injury was present in twenty-eight cases, but of these seventeen (60%) corresponded to acute subdural, leaving only eleven (39.3%) in the subacute and chronic classification. This again emphasizes that minor or trivial head injuries, without loss of consciousness, are most often the cause of the chronic lesions.

The period between the head injury or beginning of symptoms and the removal of the subdural mass, whether at operation or at autopsy, varied from two to ten weeks with an average of 7.7 weeks. There was a child with a history of head injury for ten years in whom a calcified subdural hematoma was found.

Headache was the most frequent symptom in the subacute and chronic cases and seventy-eight (93.9%) complained of headache. This was localized to the side of the subdural in twenty (24%) cases. Convulsions were reported in seventeen patients. Mental confusion, drowsiness and fluctuating level of consciousness was found in almost every case. Peet[15] had stated that mental confusion, either intermittent or continuous, was one of the most important diagnostic symptoms.

Of the findings from the neurological examination inequality of the pupils was present in twenty-five cases, being dilated on the side of the lesion. Here again Peet[15] emphasized that this is the most positive localizing sign. Dilatation of the pupil is due to the herniation of the uncus underneath the tentorium, the third nerve being then compressed in its upper portion by the posterior cerebral artery which crosses it superiorly, thus interrupting the parasympathetic fibers to the iris. Early papilledema was seen in thirteen cases, bilateral papilledema in only five, and hemiparesis in forty.

Lumbar puncture was performed in fifty-four patients, thirty-three (61%) had

FINDINGS:		
INEQUALITY OF PUPILS		25 cases
EARLY PAPILLEDEMA		13 cases
BILATERAL PAPILLEDEMA		5 cases
HEMIPARESIS		40 cases
LUMBAR PUNCTURE		54
Fluid pressure	Between 200* & 350	19 or 35.1%
	Above 350	2 or 3.8%
Fluid characteristics	Clear	45 or 87.3%
	Xanthochromic	7 or 12.7%
Proteins & Pandy	Below 50 Mg %	434 or 79.6%
	Between 50 & 90	9 or 16.6%
	Above 90	2 or 3.7%

*m.m. of water.

Table II. Physical Findings in Subdural Hematoma

normal spinal fluid pressure and in nineteen (35.1%) the pressure was between 200 and 350 m.m. of water and in two the pressure was above 350. The fluid was clear in forty-seven (87.3%) cases and bloody or xanthochromic in seven cases. Proteins and Pandy were normal in forty-three (79.6%) cases. Between 50 and 90 mgm.% in nine cases, and in two cases the proteins were 139 and 190 mgm.%, respectively.

DIAGNOSTIC STUDIES

Arteriograms (Fig. 2) were carried out in ten patients. A diagnosis of subdural hematoma was made in nine cases. Electroencephalograms (Fig. 3) were taken in twenty patients; in four patients the findings were suggestive of a subdural hematoma. X-rays of the skull (Fig. 4) revealed a shift of the pineal in five cases. Pneumoencephalograms (Fig. 5) were done in five cases, being of diagnostic help in two cases. Thirty-eight cases were correctly diagnosed, or strongly suspected, prior to the operation. The remainder of sixty-two cases had a tentative diagnosis of cerebral arteriosclerosis, post-traumatic syndrome, cerebrovascular accident, extradural hematoma, or brain tumor before surgery or autopsy.

Fig. 2 Right Carotid arteriogram showing displacement to the left of the anterior cerebral artery and "crescent" deformity of vessels of middle cerebral area, in a large chronic subdural hematoma.

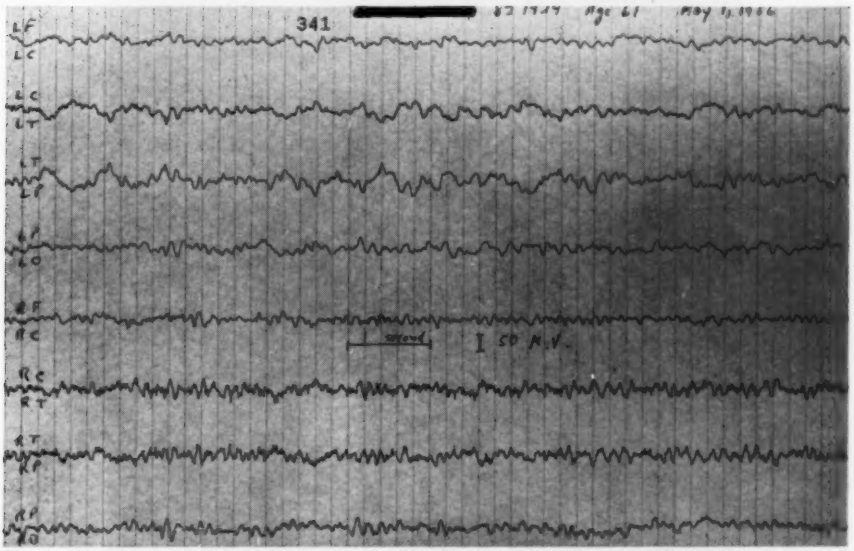


Fig. 3 There is gross asymmetry over the two hemispheres with suppression of back ground activity on the left, in association with irregular Delta activity seen more on the left temporal region. Right side essentially normal except for some minor disturbance in the form of subalpha activity. A large subacute subdural hematoma was drained.

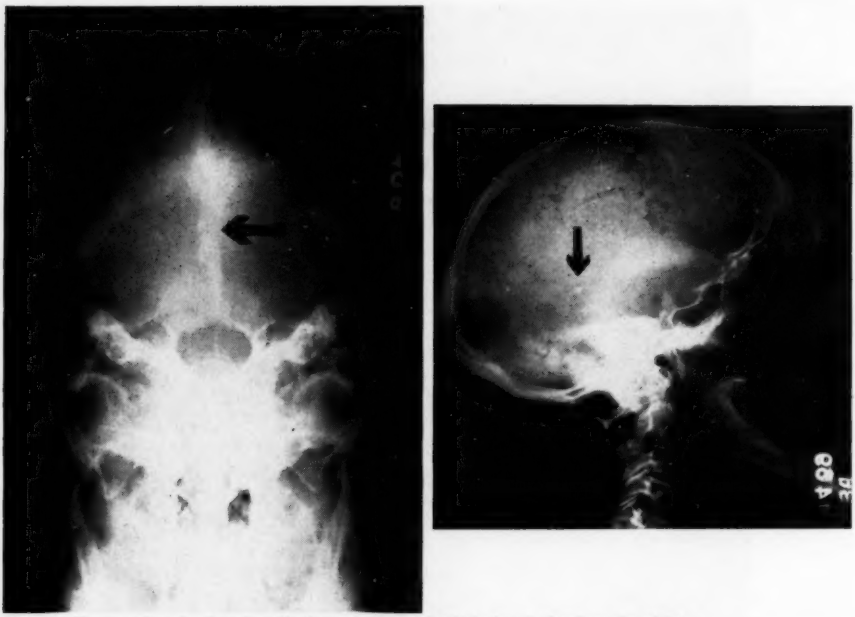


Fig. 4 Towne view A. showing displacement of calcified pineal gland to the right.
Lateral view B. shows downward displacement of pineal gland. A large fronto temporo parietal chronic subdural hematoma was removed.

Fig. 5 Pneumoencephalogram showing flattening of roof and inferior displacement of frontal horn of lateral ventricle, due to the presence of a large chronic fronto parietal subdural hematoma.

DIAGNOSTIC STUDIES:	
ARTERIOGRAMS:	10
Correctly diagnosed	9 or 90%
ELECTROENCEPHALOGRAMS:	20
Suspected diagnsosis	4 or 20%
SHIFT OF PINEAL GLAND	5
PNEUMOENCEPHALOGRAMS	5
Diagnosed correctly	2 or 40%
OPERATIVE MORTALITY:	
ACUTE SUBDURAL	55.5%
SUBACUTE SUBDURAL	4.9%
CHRONIC SUBDURAL	16.6%
PROGNOSIS:	
SURVIVAL	68 patients
Good Results	58 or 85.3%

Table III. Diagnosis Operative Mortality and Prognosis in Subdural Hematoma

OPERATIVE TECHNIQUE AND MORTALITY

The majority of adults had bilateral parietal and frontal bur holes. However, in seventeen cases an osteoplastic bone flap was necessary. In children a craniotomy was the rule, in order to remove the inner subdural membrane from the brain surface to facilitate re-expansion and normal development of the brain. Of the seventeen acute subdural lesions, thirteen died. Of the twenty-eight subacute subdural lesions, five died, and from the fifty-five chronic lesions fourteen died. Of the seventeen acute cases nine were taken to the operating room and of these five died. Of the twenty-eight subacute, twenty-one came to operation, and one died. Of the fifty-five chronic cases, forty-eight went to operation and of these nine (16.6%) died, which is slightly below some other hospitals in which 20% operative mortality in the chronic group was the average; however, Munro[16], reviewing sixty-two cases in 1934, found an operative mortality of 41.2%; however, he included both acute and chronic forms. Our over-all mortality (operative) in all forms was 19.2%.

A good prognosis depends upon an early diagnosis, before medullary or brain stem findings appear. Once this stage is reached the mortality is high. Of the sixty-eight patients that survived (Table III) fifty-eight had good results and, if adults, they were back to their usual work. If children, they had a normal somatic and mental development. The remaining ten had poor results, and patients continued complaining of headaches or had convulsive seizures. The children had slow mental development or uncontrollable seizures and had to be confined to an institution.

PATHOLOGY

A chronic subdural hematoma consists of a large collection of bloody fluid enclosed by a definite membranous sac, the outer wall being adherent to the inner surface of the dura while the inner wall lies on the arachnoid. The gross appearance is striking. Usually diagnosis is indicated by the dark bluish color of the dura, and upon opening of the dura a tense, glistening purplish membrane from which the dura can be rather easily separated, but leaving many bleeding points. The membrane varies from one to a few millimeters of thickness, the contents varies in color from bloody to chocolate and usually contains dark, partially broken down clots. After evacuation of the fluid blood and irrigation, a thin translucent bluish-green membrane is found pressed tightly against, but not adherent to the arachnoid. After removal of the inner membrane the pia-arachnoid is seen covering a congested brain cortex (Fig. 6).

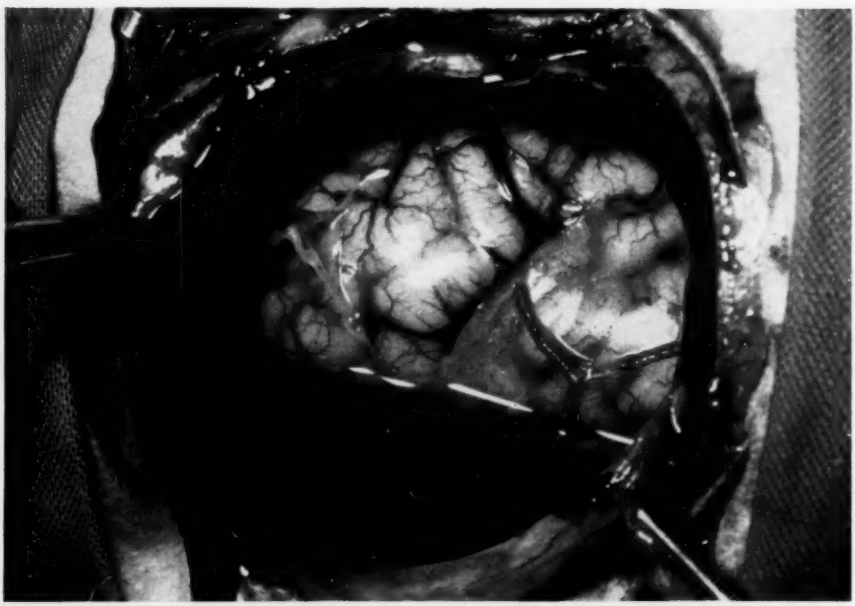


Fig. 6 Liquified chronic subdural hematoma, showing the inner membrane being partially separated from the leptomeninges, (see left upper quadrant) slightly congested cortex underneath, with marked decrease in size of the cerebral hemisphere. Outer membrane attached to the dura is seen in the inferior portion.

Microscopic examination of the outer membrane shows a layer of connective tissue adherent to the dura. The outer layer frequently shows areas of hyalinzation while on the inner surface new fibroblasts can be seen extending into the underlying clot. This membrane is quite vascularized with new formed capillaries which in the inner surface are sometimes of unusual size. Large, irregular spaces lying in a horizontal plane, lined with a single layer of "mesothelial" cells and generally containing normal blood have been repeatedly described in the outer membrane, and they seemed to be characteristic

of a chronic subdural hematoma and have not been found in hematomas situated elsewhere (Fig. 7A).

The inner membrane consists of a thin layer of connective tissue covered with a single layer of "mesothelial" cells. It is avascular and generally is stained by blood pigments (Fig. 7B). Chemical analysis shows the presence of bilirubin. This is

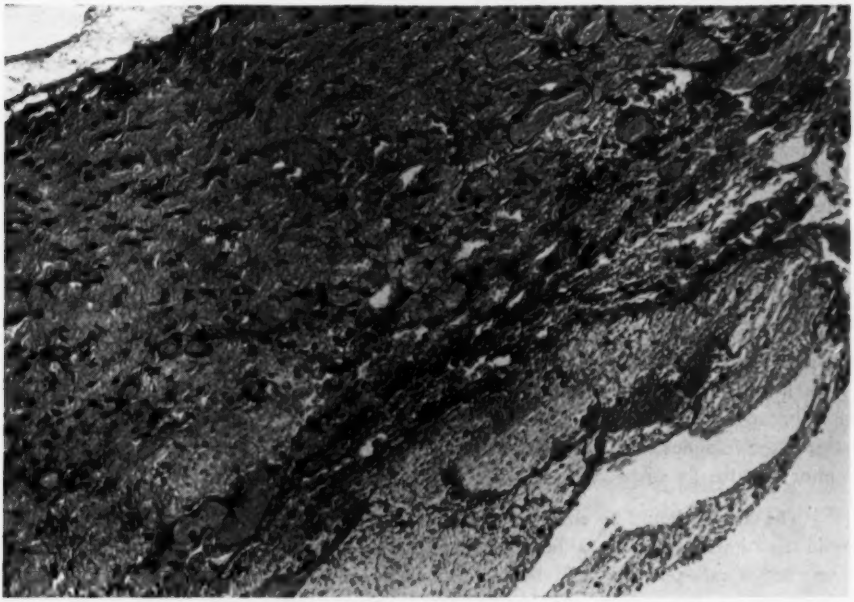
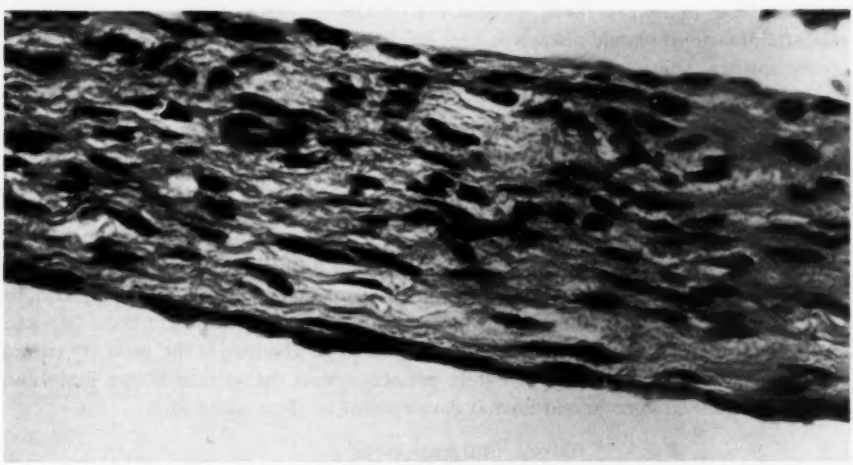


Figure 7 A.—Outer membrane showing the typical vascular lakes in the inner portion adjacent to the hematoma. These lakes can be seen better on right upper quadrant.



B.—Inner membrane show in the lower part the smooth mesothelial cell layer which lies against the lepto-meninges and makes its separation rather easy.

produced by the reticuloendothelial cells in the meninges. The origin of the "mesothelial layer" of the inner membrane has not been definitely proved, but has been stated that they arise from cells wandering from the dura to the under surface of the clot. The semipermeable nature of the inner membrane has been proved by dialyzing experiments. This lends weight to the theory of augmentation of the fluid volume by the addition of cerebrospinal fluid from the subarachnoid space. However, this space must be largely obliterated by the pressure of the hematoma.

It has been claimed by several writers that the so-called chronic subdural hematoma is not subdural but is actually an intradural lesion. The most recent to expound this belief are Wells and Dickson[17]. They offer rather convincing proof from a careful pathological study of autopsy material that the cystic hematoma lies within the meningeal layer of the dura. If this is true, it would explain the outer and inner membranes whose formation has been so obscure.

Jelsma[18] in 1930 reviewed forty-two cases from the literature with a confirmed diagnosis of chronic subdural hematoma. His average age was 39.2 years which is approximately the same as our series, 42.4 years. He stated that trauma was definite in 88% and that 98% may well have been traumatic and only two gave a history of no trauma. Here I found a marked discrepancy since we had 29% with no history of head injury. I feel this is due to the better knowledge at present of this disease and also because we are aware that subdurals are also quite frequent in older people in which the diagnosis of cerebrovascular accident, cerebral arteriosclerosis, or brain tumor are usually suspected.

The lesion should be strongly suspected in younger people who have a history of mild head injury followed by headaches and later develop drowsiness, mental confusion, hyperactive reflexes and mild hemiparesis. One should not wait until the patient is semicomatose, hemiplegic, with dilated pupils, bilateral Babinskis, which means brain stem pressure. Once he reaches this stage the prognosis is poor. In older people with a trivial head injury, or none, especially if moderate cortical atrophy is suspected, subdural hematoma should always be kept in mind since there is an increase of tension on the cortical veins which drain in the longitudinal sinus, facilitating their rupture and bleeding in the subdural spaces by any minor head injury. Here again, the headaches, mental confusion, drowsiness, and a fluctuating level of consciousness are very important helps in diagnosing this disease. The treatment should always be bilateral bur holes in the posterior parietal and frontal regions in order to drain the hematoma. In some patients an osteoplastic flap may be necessary if the patient has a thick inner or outer membrane that is inhibiting the expansion of the brain or if clotted hematoma has been left. In children the treatment is somewhat different, since subdural taps are always possible to perform, and by doing this several times the subdural space can be partially evacuated. Once the child is in good condition an osteoplastic bone flap can be turned in order to remove the membranes which in children is the most important step, since the inner membrane is tightly pressed against the surface of the brain and will impair further somatic and mental development of these children.

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SOME COMMENTS ON LIMITS AND SIGNIFICANCE OF THE "PERMISSIBLE RADIATION DOSE"

Part I — Analysis of the NCRP Recommendation on Radiation Exposure Levels

LUTHUR E. PREUSS, M.S.*

Health-physics recommendations regarding *tolerable radiation dosage,* within the last decade, have exhibited considerable change. Additionally, official pronouncements through publication of recommended levels have at times lagged behind the unofficial oral presentation. Thus, it has been the responsibility of the individual professional to keep abreast of the most recent trends by careful surveys of the literature and editorial reports.

The Executive Committee of the *National Committee on Radiation Protection* (NCRP) recently proposed a series of significant changes which, if accepted, will lower the tolerable radiation exposure limits. These recommendations of the Executive Committee are to be presented to the full National Committee on Radiation Protection. The parent committee is expected to act on approval and adoption of these new limits. A major member of the NCRP, The Atomic Energy Commission, has always put into effect the recommendations of the committee.

Indication of the official nature of the new limits may be inferred in the presentation of the recommendations by the Committee Chairman, Lauriston S. Taylor, before the American Nuclear Society, Washington, D. C., December 10, 1956. The purpose of this analysis is to interpret and place into working terms the prime points of the present day status of recommended tolerence limits. Because these limits may soon be official and since they incorporate both lower tolerable levels and new concepts of radiation protection, it is essential that the professional familiarize himself with the significance of the personal and general health-physics aspects of the recommendation. This category must include the radioactive isotope worker, radiologists, AEC employee, industrial radiographer and any other individual *exposed to any degree* of avoidable penetrating radiation.

The evolution of the status of permissible dosage limits from external sources is highly significant, when reviewed on its time base. Prior to 1929 no *coherent* system of safe radiation levels was proposed or recognized. This early era was characterized by certain instances of gross personal radiation damage. In 1934 a 'tolerance dose' of 200 milliroentgens per day or 1 roentgen per week was adopted by The International Committee on X-ray Protection. Beginning in 1936 and extending to 1948 the generally accepted tolerance value in the United States was 100 milliroentgens, per day, (measured in air). In June of 1948 a subcommittee of the NCRP lowered the then existing dose of 0.1 roentgen per day by a factor of 2 and expressed the limits in roentgens per week,

*Supervisor, Radioactive Isotope Laboratory, Edsel B. Ford Institute For Medical Research.

(0.3 roentgens per week). This extension of the time unit to seven days was significant in itself. In 1954 a comprehensive report* was published officially prescribing the limit of 0.3 roentgens equivalent man** per week, for long term whole-body exposure; a special limit of 0.6 rems per week for the skin, and a maximum of 0.3 rems per week for the blood forming organs, gonads and eye lens.

Roughly, this has been the growth and status of the recommended "maximum permissible" dosage to the present date. It must be noted that the trend in restating these values has been universally downward, with two major re-evaluations occuring within the last eight years.

The tolerable limits which have been now suggested by the NCRP set an entirely new value on occupational radiation exposure. In a sense, the new limitations are superimposed on the existing levels, and restrict or circumscribe their *carte blanche* application. In addition, a new concept of age-dosage relationship is brought out and the new limitations have been proposed from a basis of permissible gonadal exposure to individuals during their reproductive periods. A portion of this new recommendation, thus reflects a changing emphasis from *dosage to the individual* to *dosage to the population.*

This latter rationale mirrors the concern over genetic effects of radiation which must be considered statistically for the population as a whole, as contrasted with the original concept of individual, gross radiation damage.

In addition, a series of limitations based on a *yearly* and *lifetime* exposure are set up:

MAJOR TOLERANCE RECOMMENDATIONS

The four outstanding aspects of the present report may be summed up as follows:

1. The new system retains the present, basic maxima of 300 milliroentgens equivalent man, per week, with a maxima of 15 rems per year (assuming a two week period away from the source of radiation.) This also includes the previous extended-time 'penalty' unit of 13 weeks at 77% tolerance for those instances in which the weekly permissible value was exceeded.

2. One emergency dose of 25 rems is permitted in a lifetime.

3. The *maximum accumulated dose* is not to exceed an *average* of 5 rems per year. Thus, for the fifty years of life between ages twenty and seventy a total dosage exposure of 250 rems should constitute the maximum tolerable accumulation, (A formulae given, in the following discussion, elaborates on this.)

4. The Committee recommends, for the *population as a whole*, a limit of $1.4 \cdot 10^7$ rems delivered to the reproductive tissues for every 10^6 persons to age 30; or an

*U. S. Department of Commerce, National Bureau of Standards, Handbook No. 59.

**Hereinafter abbreviated as rems.

Dose in rems = (dose in rads) x RBE

average of 14 rems per person for the entire population through age 30, and one third of this value for each decade thereafter for this population unit.

The maximum acceptable weekly dose, although retained at 300 milliroentgens equivalent man, no longer may be indefinitely extended through each succeeding year. The Executive Committee has proposed a formula which ensures that the total dose is not accumulated too fast, particularly up to age 30.

This relation states, in effect, that the total accumulated dosage in rems at any age over 18 cannot be greater than five times the number of years the individual's age is above age 18.

Thus:

$$D = (A - 18) \cdot 5 \text{ rems.}$$

where:

D = total accumulated dosage in rems.

A = Individual's age.

For example, a 29 year old individual must not accumulate in excess of 55 total rems; [(29 — 18) · 5].

Two important aspects of this must be stressed. Firstly, under age eighteen no avoidable exposure is acceptable. Secondly, this formula reduces the total accumulated exposure considerably during the younger child-bearing ages and allows some margin for the years beyond this period.

This application immediately produces a large gap between the old limit and the new. For example, consider two workers involved from age 20 to 70 in industrial atomic energy exposures. Assume that both have exposures just up to, but not exceeding, the permissible limits. Worker "A" uses the old system of a straightforward 300 millirems per week and worker "B" uses the new recommendation outlined above. "A" at age 70 then has accumulated 750 rems while "B" has a total of only 250.

Worker "A" in addition may have begun exposure at an early age, say age 16. Whereas, "B" by the new system cannot begin exposure until age 18 and by the inherent nature of the limits of the system is encouraged to avoid all possible exposure until age 30 or 40. Thus, the very aura of the new proposals may keep early age dosages to a small fraction of those under the old system.

Inherent in this system is the concept of an unused 'bank' of exposure. By the new system, an individual who from age 20 to 25 accumulates only a total of 1 rem per year, has used up only 5 rems of his maximum of 25 for this 5 year period. He has 20 rems in the 'bank', so to speak, and on his sixth year may take a total (if emergency dictates) of 15 rems without exceeding, or *overdrawing*, his 'account'. In fact, in the above case, the dosage account still shows a balance of 10 rems at the end of the sixth year.

It is obvious then, that individuals who begin radiation exposure at a later age will have a reserve (in rems) equivalent to five times the difference between 18 and the

individuals age, at the time of beginning exposure.

The intent and prime result of the tightening of total dosage from age 18 to 40 has resulted in extra safeguards for the worker during the critical reproductive years. This, of course, ties in with the fourth proposal for a maximum permissible population dosage.

For the professional and industrial workers who are exposed to ionizing radiation, this new set of regulations will, in general, mean a closer and more restrictive operation§ in which exposures, where routine and maximal, must be cut by about one third. The radiological safety officer must now think in terms of the old weekly permissible dosage and also in terms of a new concept of yearly dosage which is not directly proportional to the weekly dosage.

The Committee has stressed, that design and the mode of operation of any radiation facility, particularly one where routine radiation hazard is present, must be such that, radiation to workers does not approach too closely to limits being recommended. The radiation "account" of each worker must, under the ideal condition, show a reserve 'banked' for future use. This situation is particularly stressed where the worker is between 18 and 40.

The new concept of yearly and lifetime tolerances places an emphasis on a record system for all workers which is audited on the basis of these time units. An additional implication is that the worker should have such accurate records avaiable when changing positions. Needless to say, such records will be of immense aid in the future in evaluating the overall genetic effect and the efficiency of these regulations. This lack of coherent information has been one of the major stumbling blocks in firmly fixing such permissible levels for radiation exposure, and may account for some of the repeated lowering of limits in the last decade.

In addition to elimination of the rule for double exposure for over age 45, the new rules set limitations of 5 rems to the blood forming organs, 5 rems to the gonads, 5 rems to the lens of the eye and 10 rems to the skin, for the *yearly* tolerable exposure. This again is a reduction of the limits found in the 1954 regulations.

It is significant to recognize that these levels are not modified by the allowance for an emergency exposure of 25 rems once in a lifetime or by radiation exposure received for medical reasons. The official pronouncements of the committee as published in 1954 will still stand with the exception of the over-riding regulations outlined herein.

SUMMARY:

For all those working in the presence of ionizing radiation this new recommendation brings out the present fluidity of the values for the permissible dose. The recommendation reflects the very conservative attitudes which stem from the National Academy of Science's report* on the effects of atomic radiation on man, and particularly mirrors its concern over genetic effects. The individual worker would

§The NCRP allows a 5 year 'transition' period.
*1955 NAS report.

be well advised at this time to review critically the status of exposure and the personal records maintained. The auditing of an additional section for a reserve or unused exposure will be essential.

The continued emphasis on lower dosage rates to the blood forming organs, skin, lens of the eye and gonads may be a limiting factor for certain workers experiencing exposure to specific radiation species or under conditions which may selectively effect these organs.

The major point which may need clarification is the retention of the maxima of 0.3 rems per week and 15 rems per year, with the over-riding stipulation of an average of only 5 rems per year. This concept is given in terms of first, a *maxima,* and second, in terms of an *average.* For example, it will be possible for an individual to take dosages of 0.3 rems per week, from time to time, as long as his *average* over his work history does not exceed 5000 millirems per year. Thus, the worker may for a few years attain the yearly maximum of 15 rems, but he must balance these years with ones of low dosage so that for his total working history his average is 5 rems per year or less.

Although the new rules are not modified by dosage necessitated for medical expediency, the attitude is presented that the prudent employer must take any especially significant medical dosage into account in the assignment of the individual to work which involves radiation. This implies new responsibilities for the medical professional at least in the assessment of whole body radiation and the consequent notification of the employer where the patient's activities are known to involve radiation hazards.

TABLE I

MAJOR ASPECTS OF THE NEW DOSAGE SYSTEM

ITEM	1954 NCRP Pronouncements	1957 Recommendations	Remarks on New System
Whole body weekly dosage	0.3 rems	Still holds at 0.3 rems but only as a *maxima.*	*Average* about 16 mrems per day. 0.3 rems exposure per week should be balanced with periods of low dosage.
Whole body yearly dosage	15 rems	Still holds but only as *Maxima. Average* dose must be '5 rems' per year (or below).	*Average* exposures must not exceed 100 mrems per week.
Skin, yearly dosage	30 rems	*Average* of 10 rems.	Factor of 3 reduction. 200 mrems per week.
Eye lens, gonads, blood forming tissue, yearly dosage.	15 rems	*Average* of 5 rems.	Factor of 3 reduction. 100 mrems per week.

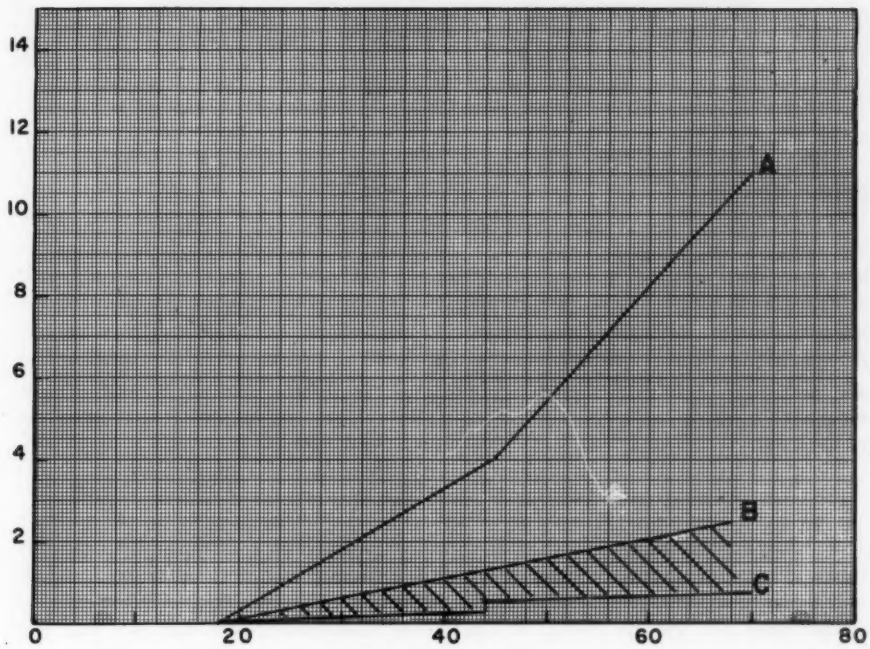

Figure No. 1

A hypothetical situation for radiation workers A, B and C is schematically outlined here, to illustrate for one case the effect of the new proposals as contrasted with the old system. Age in years is plotted on the abcissa, and the total accumulated dose in rems on the ordinate has been divided by 10^2. Worker A begins exposure to man-made radiation at age 18 along with workers C and B. However, A observes the permissible dosage limits set up by the NCRP in their 1954 publication. Worker A is exposed to the maximum permissible dosage throughout his work history. Note that he doubles his exposure at age 45 and at age 70 terminates this type of work with a possible 1105 rems total accumulated exposure. Worker A without doubling his dosage at age 45 would receive a total of 780 rems at age 70.

Worker B, observing the new proposals, averages the maximum dosage recommended, of 5 rems per year, for his entire work history and at age 68 has accumulated 250 rems and should then terminate his exposure according to the new proposal.

Worker C not only observes the letter of the new proposal but, in keeping his total dosage down to the lowest possible value (here given at 1 rem per year), attempts to follow the *intent* of the new system as well. The shaded area between B and C illustrates the reserve "banked" by C. At the end of 26 years C has a reserve of 96 rem. At age 44 worker C is free to take a necessary exposure of 24 rem, shown as the vertical rise in his plot. This expends his once per life time emergency exposure. Immediately therafter he resumes exposure at his initial low rate. At age 70, worker C has accumulated 76 rems (including the emergency). This curve C would be a close representation of the practical, working, life-time, dosage history of a clinical or industrial isotope laboratory worker, radiologist or industrial radiographer where the proper health physics measures have been observed.

THE MILK-ALKALI SYNDROME

CASE REPORT

ROBERT J. PRIEST, M.D.,* RICHMOND W. SMITH, M.D.,**
AND W. EARL REDFERN, M.D.,**

Burnett and his co-workers[1] in 1949 described a syndrome which occurred in patients consuming excessive amounts of milk and absorbable alkalies for symptoms of peptic ulcer. In addition, Burnett's series of six male patients presented other interesting features which included, hypercalcemia without hypercalcuria or hypophosphatemia, normal serum alkaline phosphatase levels, marked renal insufficiency with azotemia, mild alkalosis, calcinosis including an ocular lesion, and improvement following a restriction in dietary calcium and the elimination of alkali therapy. Burnett recognized that primary hyperparathyroidism could not be excluded with certainty in all patients. This difficult differential diagnosis has been recognized in several later reports[2,3,4,5]. The following history presents such a problem of differential diagnosis in a patient with chronic duodenal ulcer and bilateral nephrolithiasis.

CASE REPORT

L. P. No. 417503, a 59-year-old male was first seen at Henry Ford Hospital in 1947 when he was 49 years of age. His chief complaint was gross hematuria. He was found to have bilateral ureteral calculi and right renal calculi. The left kidney function was diminished in the intravenous pyelogram study. However the voided urine was concentrated to a specific gravity of 1.021. The blood hemoglobin was 14.6 gm. His past history included a chronic duodenal ulcer which had bled twenty-five years previously. The ulcer had been self-treated with milk in quantities up to two quarts daily. Sodium bicarbonate had been consumed daily for many years and there were weeks when he had purchased two half-pound boxes of the antacid, representing an approximate daily dose of 65 grams.

In 1953, symptoms of polyuria, polydipsia, weakness and pain in the legs led to his hospitalization. Blood pressure was 190/100. There was slight pedal edema. A specific gravity of 1.006, traces of albumin and an occasional red blood cell were found in the urinalysis. The hemoglobin was 11.8 gm. and total serum bilirubin, 0.23 mg. Bromsulfalein retention and the liver flocculation tests were negative. The serum albumin was 4.3 and globulin 1.9 gm., while serum calcium was 11.8 and phosphorus 4.0 mg. Basic phosphatase was 1.42 Bodansky units. Serum sodium was 139, chlorides 79, potassium 4 and CO2 capacity 33.8 m.Eq per liter. The plasma non-protein nitrogen was elevated to 130 mg. percent. The standard urea clearance was 12 cc. and 11 cc. per minute. Urine culture grew a non-hemolytic streptococcus and Bacillus subtilis. The stool was negative for occult blood. An electrocardiogram was normal. Because of a deeply pigmented skin, Addison's disease was considered and the eosinopenic response to ACTH administration was determined. The drop in cell count from 172 to 125 was subnormal, but the studies pertaining to this diagnosis were not carried further.

*Associate, Division of Gastroenterology.
**Physician-in-Charge, Division of Endocrinology.
***Associate, Division of Metabolism.

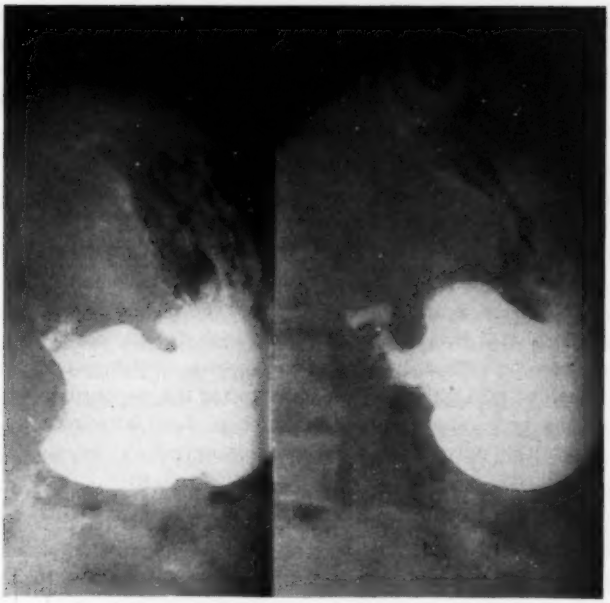

FIGURE 1 Obstructing duodenal ulcer deformity with retention of barium in the stomach.

FIGURE 2 Bilateral nephrolithiasis and o dense osseous sclerosis of the sacroiliac joints.

The heart was found to have a hypertensive configuration by roentgen examination of the chest. X-ray studies of the skull and colon were normal. A deformed cap was seen in the x-ray of the duodenum and retention of barium in the stomach indicated an obstructing cicatrix (Fig. 1). Bilateral nephrolithiasis and an osseous sclerosis of both sacroiliac joints were seen in the roentgen film of the abdomen (Fig. 2).

A diagnosis of the milk-alkali syndrome was made, and the patient was cautioned to avoid soda bicarbonate. The blood pressure gradually returned to normal. One month later he was symptom-free and the NPN had reduced to a level of 24 mg. percent. Subepithelial deposits of calcium, concentric with the limbus, were found later by slit lamp examination of his cornea. During subsequent office visits a succussion splash was heard in the upper abdomen. The highest acidity was 88 degrees of free hydrochloric acid in a fractional gastric analysis. Various types of aluminum hydroxide gels were prescribed, but these were discarded by the patient. Preparations containing magnesium salts caused a burning distress in the epigastrium; while aluminum phosphate gel and preparations containing calcium were interdicted because of the renal dysfunction. Dihydroxy aluminum aminoacetate gel was tolerated fairly well.

The patient remained free from ulcer distress and symptoms of renal failure. However the hemoglobin dropped to 9 grams and hematocrit to 34. In early 1955 the non-protein nitrogen was 73 mg. percent. The 24-hour urinary calcium excretion was 185 mg., although the collection was not made while he was on a low calcium intake. A Sulkowitch test of the urine was not strongly positive. More detailed metabolic studies were requested of the patient, but he was unable to complete them.

In August, 1955, the patient ingested sodium chloride tablets during a week of travel in hot weather. His weight abruptly increased four pounds and he became dyspneic and orthopneic. Hypertension was again present, the blood pressure being 190/100. A specific gravity of 1.005, traces of albumin and 2-5 red blood cells per H.P.F. were found in the urinalysis. The blood hemoglobin was 9.9, serum albumin, 5.0 and globulin, 1.8 gm. The serum CO2 was 16.2 and chlorides, 104 m.Eq. per liter. Maximal urea clearance was 17 cc. per minute. A phenolsulfonphthalein excretion was 10 percent. The electrocardiogram was normal.

After a short period of sodium restriction, the patient was able to resume his activities without symptoms. During the following year his hemoglobin fell to 8.4 gm. and he again complained of fatigue. In August, 1956, he was transfused with 1000 cc. of whole blood after therapy with ferrous sulfate had failed to correct the anemia. Except for pruritis, he has continued free from symptoms. The skin has remained deeply pigmented and small pruritic papules on the back and shoulders have appeared on two occasions.

DISCUSSION

This patient has presented essentially all the clinical and metabolic features of the original description of the milk-alkali syndrome[1]. The history was well established that excessive milk and absorbable alkali were used over many years for symptoms of a chronic duodenal ulcer. It is significant that ocular band keratopathy was noted during slit-lamp study, since this was the only physical finding common to all of Burnett's six patients and to 16 of the 21 patients reviewed by Kessler[4]. Renal calculi

were present bilaterally and an ossifying sclerosis was observed in the x-rays of the sacro-iliac joints. There were no findings in the skeletal x-rays which suggested hyperparathyroidism.

Although there was impaired renal function when the patient was first seen, a definite metabolic alkalosis was indicated by a serum CO2 level of 33.8 m.Eq. per liter. As renal function was compromised further, and the absorbable alkali was withdrawn, the alkalosis was superceded by an acidosis of moderate severity. The renal insufficiency was demonstrated by the urea clearance tests and clinically on two occasions by the development of azotemia, hypertension and anasarca following the ingestion of excessive salt.

We lack clear evidence of antecedent renal impairment. However, if present it was not advanced, since extensive renal or ureteral calculi would not be expected to develop in a kidney with markedly curtailed excretory function. We believe the hypercalciuria and hyperphosphaturia of excessive milk ingestion was possible only with adequate renal function. Precipitation in urine containing such high mineral content would be facilitated greatly by the chronic alkalosis, just as in urine made alkaline by urea-splitting organisms. There is evidence that milk and absorbable alkali adversely affect kidney function[8], and that the damage from alkalosis may be aggravated by excessive calcium loads[2].

Other metabolic features included a moderate hypercalcemia and normal phosphatemia while the patient received a standard hospital diet. The Sulkowitch reaction and 24-hour urinary calcium excretion were not excessive for an unrestricted diet. The serum albumin concentration was increased, as noted originally by Burnett[1]. Failure to obtain further metabolic data resulted from the patient's unwillingness to re-enter the hospital for study.

The final feature of the similarity between our patient and those of Burnett's study is the clinical improvement after eliminating the absorbable alkali and excessive milk. A deeply pigmented skin and pruritic papules on his back and shoulders have been observed, similar to lesions reported by Burnett[1] and Kyle[2]. The azotemia, hypertension and edema have cleared without specific therapy other than sodium restriction. Permanent renal damage probably has resulted since there is a metabolic acidosis and a chronic hypochromic anemia which has been refractory to treatment. No occult bleeding from the duodenal ulcer has been found. The electrocardiographic abnormalities that may accompany this syndrome[7] were not present.

As emphasized by other authors, the differentiation of the milk-alkali syndrome from hyperparathyroidism may be difficult. Kyle[2] stated that an improvement on a diet low in calcium and absorbable alkali is the only differential feature. The observations of Chambers and associates[9] that the hypercalcemia of hyperparathyroidism may be accentuated by a restriction in dietary phosphorus suggests that such dietary restrictions may have diagnostic value. The finding of a metabolic alkalosis which clears when the patient restricts alkali ingestion does not decisively eliminate the diagnosis of hyperparathyroidism, since this treatment might be adopted by a patient with hyperparathyroidism who also has a peptic ulcer. The frequency of ulcer-like symptoms in patients with hyperparathyroidism has been recognized as a major confusing feature in the differential diagnosis.

The presence of calcinosis and band keratopathy of the eye are not strongly distinguishing features, but they tend to favor either the milk-alkali syndrome or vitamin D poisoning. Assuming the same degree of renal impairment in each, the patient with the milk-alkali syndrome likely would have extra-skeletal calcification earlier than the hyperparathyroid patient. Dworetzky[10] and Poppel et al[11] have observed improvement in patients with calcinosis when a low calcium diet was employed.

When clinical features and blood indices have suggested or strongly indicated a diagnosis of hyperparathyroidism, the finding of hypercalciuria has been the usual supportive or confirmatory index. With advanced renal failure in hyperparathyroidism however, urinary calcium may be low[3] and phosphate retention may mask a previously diagnostic hypophosphatemia[5]. In the presence of advanced renal insufficiency, surgical exploration of the parathyroids and critical histological study of the sections may be necessary to differentiate the two disorders. More recently the tolerance test of intravenous calcium[3] and the phosphate reabsorption test have been employed. The limited data regarding the use of such procedures in the study of patients with the milk-alkali syndrome suggest that they were of diagnostic value[3]. Also, renal insufficiency is likely to modify the tubular handling of phosphate and thus limit their diagnostic value.

We believe the evidence presented in the case report of our patient favors a diagnosis of the milk-alkali syndrome rather than a diagnosis of hyperparathyroidism. The two most helpful though not decisive observations have been the azotemia with alkalosis and the continuing improvement of the patient when he was given a diet low in calcium and absorbable alkali.

SUMMARY

A case report of the milk-alkali syndrome is presented to illustrate the metabolic abnormalities of this disease and its difficult differentiation from hyperparathyroidism.

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INTERNATIONAL SYMPOSIUM

RETICULAR FORMATION OF THE BRAIN

March 14, 15, 16, 1957

The professional staff of the Henry Ford Hospital with the initial advice and support of the Board of Trustees and Dr. Robin C. Buerki, Executive Director, of the Henry Ford Hospital, is sponsoring an international symposium on the subject Reticular Formation of the Brain. This symposium will be held at the Henry Ford Hospital, March 14, 15, and 16, 1957, in the Clinic Auditorium. The preliminary program follows and has been prepared with the help of the advisory members:

PROGRAM COMMITTEE

Advisory Members:

Chairman	
Horace W. Magoun	Department of Anatomy, Medical School University of California, Los Angeles, California.
J. Douglas French	Veterans Administration, Long Beach, California.
Herbert H. Jasper	Montreal Neurological Institute, Montreal, Quebec.
Russell N. DeJong	Department of Neurology, University of Michigan, Ann Arbor, Michigan.
Ralph W. Gerard	Mental Health Institute, University of Michigan, Ann Arbor, Michigan.
Arthur A. Ward, Jr.	School of Medicine, University of Washington, Seattle, Washington.

LOCAL MEMBERS

Co-Chairmen

Robert S. Knighton	Division of Neurosurgery, Henry Ford Hospital.
Lorne D. Proctor	Division of Neurology and Psychiatry, Henry Ford Hospital.
Secretary	
William C. Noshay	Section of Neurology, Henry Ford Hospital.
Russell T. Costello	Department of Medicine (Neurology), Wayne University, Detroit, Michigan.

PRELIMINARY PROGRAM

Thursday Morning Session I 9:00 — 12:30 P.M.

8:30 A.M. Remarks of Welcome

Robin C. Buerki, Executive Director, Henry Ford Hospital.

Chairman: *Herbert H. Jasper,* Montreal, Canada.

The Neuroanatomy of the Reticular Formation

9:00 Some Ascending Pathways from the Brain Stem Reticular Formation
Walle J. H. Nauta, Washington, D. C.
Co-Author: *H. G. J. M. Kuypers,* Baltimore, Maryland.

9:30 Substrates for Integrative Mechanisms in the Brain Stem Reticular Core
Arnold B. Scheibel
Co-Author: *Madge Scheibel,* Los Angeles, California.

10:00 Discussion Designated
Jerzy Olszewski, Montreal, Quebec.

10:30 Intermission

The Physiology of the Reticular Formation

INTRINSIC EFFECTS OF RETICULAR FORMATION

10:45 Temporal Patterns of Discharge in Individual Reticular and Cortical Neurons
V. E. Amassian, Seattle, Washington

11:00 Discussion Designated
Horace W. Magoun

EFFECT OF ANAESTHETICS AND 'TRANQUILLIZING' DRUGS

11:15 Drug Action on Pathways Involving the Reticular Formation
Keith F. Killam, Los Angeles, California.

11:30 The Central Action of Certain Drugs in Relation to the Reticular Formation of the Brain
Phillip B. Bradley, Birmingham, England.

ELECTROENCEPHALOGRAPHY

11:45 Studies of Evoked Potentials in Man and Cat
Mary A. B. Brazier, Boston, Massachusetts.

12:05 Discussion Designated
Harold Himwich

12:30 Luncheon

THURSDAY AFTERNOON SESSION
2:00 — 5:00 P. M.

Chairman: *Russell N. DeJong,* Ann Arbor, Michigan

The Physiology of the Reticular Formation

AFFERENT INPUT

2:00 Central Control of Afferent Activity
Robert B. Livingston, Bethesda, Maryland.

2:30 The Relation Between Spinoreticular and Ascending Cephalic Systems
James L. O'Leary, St. Louis, Missouri.

3:00 Discussion Designated
John D. French, Long Beach, California.
Chairman: *Ralph W. Gerard,* Ann Arbor, Michigan.

NEUROENDOCRINE ASPECTS OF RETICULAR FORMATION

3:45 The Reticular Formation, Stress and Endocrine Activity
Geoffrey, W. Harris, London, England.

4:15 Activation and Blockade of the Release of Pituitary Gonadotrophin as influenced by the Reticular Formation
Charles H. Sawyer, Los Angeles, California.

4:30 Hypothalamic Localization for the Control of Various Endocrine Secretions
David M. Hume, Richmond, Virginia.

4:45 Discussion Designated
Robert W. Porter, Washington, D. C.

6:30 Buffet Dinner

The Development of Ideas Relating the Mind with the Brain
Horace W. Magoun, Los Angeles, California.

FRIDAY MORNING SESSION
9:00 — 12:30 P. M.

Chairman: *John D. French,* Long Beach, California

SPINAL MECHANISMS

9:00 Efferent Functions of the Reticular Formation
Arthur A. Ward, Seattle, Washington.

9:30 Relations of the Reticular Formation to Muscle Spindle Excitation
Earl Eldred, Los Angeles, California.

9:45 A Pharmacological Analysis of Some Reticular and Spinal Cord Systems
Edward F. Domino, Ann Arbor, Michigan.

10:00 Discussion Designated
Warren S. McCulloch, Cambridge, Mass.

10:30 Intermission

ASCENDING TRACTS AND THEIR CEPHALIC INFLUENCE

10:40 Action of the Reticular System on Cerebral Cortex
Herbert H. Jasper, Montreal, Canada.

11:00 Enduring Potential Changes Associated with Stimulation of Brain Stem and Thalamus
A. Arduini, Pisa, Italy.

11:20 Discussion Designated
Henri Gastaut, Marseilles, France.

11:35 Humoral Affects on the Brain Stem Reticular Formation
Paul Dell, Paris, France.

11:55 Cortical Excitability and Cortical Circulatory Homeostasis
David H. Ingvar, Stockholm, Sweden.

12:15 Discussion Designated
Robert Livingston, Bethesda, Maryland.

12:30 LUNCHEON

FRIDAY AFTERNOON SESSION
1:45 — 5:30 P. M.
Chairman: *Arthur A. Ward,* Seattle, Washington

The Physiology of the Reticular Formation

NEOCORTEX-INTRINSIC CORTICAL

1:45 The Place of Cortex in the Reticular System
George H. Bishop, St. Louis, Missouri.

2:05 Coordination of Specific and Unspecific Afferent Impulses at Single Neurons of the Visual Cortex
R. Jung, Freiburg, Germany.

2:25 Organization of Excitatory and Inhibitory Synaptic Electrogenesis in the Cerebral Cortex
Dominick P. Purpura, New York City, N. Y.

2:45 Activity of Inter-neurones in the Neocortex
Choh-Lu Li, Bethesda, Maryland.

NEOCORTEX-CORTICIFUGAL

3:00 Cortical Influences Upon Function of Reticular Formation
John D. French, Long Beach, California.

3:25 Discussion Designated
Herbert Jasper, Montreal, Canada, *Harry Grundfest,* New York N. Y.

3:45 Intermission

NEOCORTEX-CONDITIONED LEARNING

4:00 The Reticular System and Perceptual Discrimination

Donald B. Lindsley, Los Angeles, California.

4:20 Modification of Learning by Lesions and Stimulation in the Diencephalon and Related Structures
W. R. Ingram, Iowa City, Iowa.

4:40 Some Electrical Events Involved in the Formation of Temporary Connections
Frank Morrell, Mineapolis, Minnesota.

5:00 Role of Reticular Formation in Acquisition of Conditioned Behavior
Henri Gastaut, Marseilles, France.

5:20 Discussion Designated
Helen Mahut, Montreal, Quebec.

7:00 BANQUET

The Dawn of Medicine

Wilder Penfield, Montreal, Canada.

SATURDAY MORNING SESSION
9:00 — 12:30 P. M.

Chairman: *Horace W. Magoun,* Los Angeles, California

The Physiology of the Reticular Formation

LIMBIC SYSTEM AND HYPOTHALAMUS

9:00 The Function of the Reticular Formation and its Related Systems
John D. Green, Los Angeles, California.

9:20 Organization of the Rhinencephalon
Ross W. Adey, Victoria, Australia.

9:40 Central Nervous System Regulation of ACTH Secretion
John W. Mason, Washington, D. C.

10:00 Discussion Designated
Peter Gloor, Montreal, Canada.

10:30 Intermission

Psychological Actions, Drive and Reward Concepts — Auto Stimulation

11:00 Self Stimulation Experiments and Differentiated Reward Systems
James Olds, Los Angeles, California.

11:20 Temporal and Emotional Factors Related to Electrical Self Stimulation of the Limbic System
J. V. Brady, Washington, D. C.

11:40 Primary Emotional States Induced by Subcortical Electrical Stimulation in the Brain as Opposed to "Sham Emotions" (Ransom Bard) or "Pseudo-affective" (Masserman) states
John C. Lilly, Bethesda, Maryland.

12:00 Discussion Designated
Seth Sharpless, New Haven, Connecticut.

12:30 LUNCHEON

SATURDAY AFTERNOON SESSION

2:00 — 4:00 P. M.

Chairman: *Henri Gastaut,* Marseilles, France

2:00 Behavior and Consciousness as Related to the Reticular Formation
Sir Geoffrey Jefferson, Manchester, England.

2:40 Discussion Designated
Wilder G. Penfield

3:00 FINAL SUMMARY
Ralph W. Gerard, Ann Arbor, Michigan.

INTRODUCTION TO NEW STAFF MEMBERS

VICTORIA LING BECKETT, M.D., joined the Department of Medicine as a part time Associate in Medical Clinic No. 6, on January 15, 1957. Dr. Beckett was born in China and is 33 years old. She received her B.S. from Mt. Holyoke College and her M.D. from the University of Michigan in 1949. After internship and six months of Residency in Internal Medicine at the Minneapolis General Hospital, Dr. Beckett completed a three year Fellowship in Internal Medicine at the Mayo Clinic. From 1954 to 1955 she was an Assistant in Medicine at the Mayo Clinic and since coming to Detroit has been a Junior Associate in Medicine at Detroit Receiving Hospital. She is a member of the Wayne County Medical Society. Dr. Beckett is married to a physician and lives at 10410 E. Jefferson, Detroit.

RODMAN EASTMAN TABER, M.D., joined the Department of Surgery as Associate in Thoracic Surgery on November 1, 1956. Dr. Taber, a native of Marshalltown, Iowa, is 37 years old. He received his B.A. and M.D. from State University of Iowa, the latter in 1943. Following internship at the Pennsylvania Hospital, Dr. Taber spent 3 years as a Medical Officer, Army Medical Corps, in the Pacific Theater. From 1947 to 1950 he completed a surgical residency at the Burlington County Hospital, Mt. Holly, N. J., and following this had one year of Pathology residency at the State University of Iowa College of Medicine. From 1951 to 1952 Dr. Taber completed his Thoracic Surgery residency at Iowa, joining the staff of that institution as an Instructor in Thoracic Surgery in 1952. He was Assistant Professor, Department of Surgery, Thoracic Division, prior to leaving to join our staff. Dr. Taber is Certified by the American Board of Surgery and the American Board of Thoracic Surgery. He is a member of the American College of Surgeons, the American Association for Thoracic Surgery, and the American College of Angiology. He is married with three children and lives at 27915 Sunset, Lathrup Village.

MARY ROSE COSTELLO, M.A., PhD., joined the Division of Otolaryngology as an associate in the section of Audiology on September 15, 1956. She is a native of Jacksonville, Illinois. Dr. Costello received her B.S. from Washington University in 1939, her M.A. from Northwestern University in 1947 and a Ph.D., from the same institution in 1956. From 1939 to 1953, she was director of the Junior League School for speech correction in Atlanta, Georgia and an instructor in speech correction in Audiology at Emory University, Atlanta, Georgia. She has been associated with the Audiology Department of Northwestern University from 1953 to 1956. She has received her certification in Hearing from the American Speech and Hearing Association. Dr. Costello lives at 1533 Roselawn Avenue, Detroit.

ABSTRACTS OF RECENT PUBLICATIONS OF THE PROFESSIONAL STAFF OF THE HENRY FORD HOSPITAL AND THE EDSEL B. FORD INSTITUTE FOR MEDICAL RESEARCH

THE CENTRAL TEGMENTAL BUNDLE; AN ANATOMICAL AND EXPERIMENTAL STUDY IN THE MONKEY. J. Bebin. J. Comp. Neurol. 105:287, 1956.

The central tegmental bundle is a complex of fibers of varying lengths, partly chains of neurons linking to some extent the diencephalic and mesencephalic centers, and chiefly a group of long fasciculi enriched with the mesencephalic components, between the tegmentum of the brainstem and the inferior olive. During their course, these fascicles are joined by rubro-olivary, tegmento-olivary and dentato-olivary fibers. The combined bundle ends in the inferior olivary complex, in the central reticular substance and in the nucleus ambiguus. A few fibers continue into the cervical cord.

The stimulation of the central tegmental bundle by mediation of the stereotaxic instrument elicited movements of the palatal musculature, raising and deviation of the uvula and elevation and contraction of the soft palate toward the side stimulated. These movements were sometimes accompanied by a bilateral rhythmic contraction of the palate similar to the palatal nystagmus seen in human patients. These responses were frequently associated with changes in respiratory frequency, and occasionally with ocular or facial responses.

COMPARATIVE EVALUATION OF INTRAVENOUS PYELOGRAPHIC MEDIA. A. W. Bohne and D. R. Drew. A.M.A. Arch. Surg. 73:927, 1956.

A blind comparative study of 800 cases of intravenous pyelography with use of sodium acetrizoate (Urokon sodium) 50% and 70%, sodium diprotizoate (Miokon sodium) 50%, diatrizoate (Hypaque sodium) 50%, and a combination of the sodium and methylglucamine salts of ditrizoate (Renografin) 76% is reported. The types and percentages of reactions and the quality of the resulting pyelograms are recorded. The results seem to indicate that there are significantly fewer reactions to be expected with the use of sodium diprotrizoate 50%, diatrizoate sodium 50%, and Renografin 76% than with the use of sodium acetrizoate 50% and 70%, whereas the quality of the resulting pyelograms is approximately the same for all of the media used in the study.

ONE-STAGE TOTAL COLECTOMY FOR ULCERATIVE COLITIS. L. S. Fallis. Am. J. Surg. 92:696, 1956.

The thinking regarding the surgical treatment of ulcerative colitis has now crystallized into the concept that when operation is indicated a permament ileostomy should be fashioned and the entire colon and rectum should be removed. Elimination of the perineal portion of the operation avoids the change in position of the patient which is often conducive to lowering of blood pressure and the onset of shock. Furthermore, there is less blood loss since there is only minimal perineal dissection. The resulting perineal wound heals promptly, thus eliminating the long delay usually

associated with perineal resection. This technic has been performed on twenty-nine patients (sixteen one-stage operations and thirteen two-stage operations). There were no immediate postoperative deaths in the series, but one patient died on the twenty-third postoperative day following a secondary operation for intestinal obstruction due to volvulus. One-stage removal of the entire colon, rectum and anal canal through an abdominal incision is a feasible operative procedure in selected patients.

CONDYLECTOMY FOR THE PERSISTENTLY PAINFUL TEMPOROMANDIBULAR JOINT. F. A. HENNY AND O. L. BALDRIDGE. J. Oral Surg. 15:24, 1957.

An operative procedure for surgical relief of persistent temporomandibular joint pain has been developed. Twenty patients who had failed to respond to conservative therapy we subjected to high mandibular condylectomy with preservation of the meniscus, condylar neck and ligamentous attachments. All these patients have had complete and lasting relief from pain, and function has returned to normal rapidly with no evidence of facial nerve damage. Very slight deviation of the mandible in its extreme open position was observed in 50 per cent of the patients, but was too insignificant to be of clinical importance. Operative interference is indicated only when comprehensive conservative therapy has failed to eliminate joint pain.

FIBRINOGEN-FIBRIN CONVERSION SYNDROME. C. P. HODGKINSON. West. J. Surg., Obst. & Gynec. 64:658, 1956.

The clinical purview of the fibrinogen-fibrin conversion syndrome has rapidly extended. Identified first with abruptio placentae, the syndrome soon included long intrauterine retention of a dead fetus and amniotic fluid embolism. In the realm of suspicion now fall isolated clinical conditions, such as the generalized Shwartzman reaction, Sheehan's disease, bilateral renal cortical necrosis, hemolytic blood reactions, and trauma, either surgical or accidental. Theory holds thromboplastin to be the alleged etiological agent and hyperthromboplastinemia the physiopathologic mechanism. Shock is assumed to be caused by occlusion of the terminal arterioles with insoluble fibrin gel; and hemorrhage, from critical depletion of fibrinogen. For perspicuous understanding of thromboplastin-induced disease, agreement upon the definition of terms and the differentiation of fact from fancy are necessary. It is essential to ask such questions as: what is thromboplastin, how and where is it formed; what is fibrinogen, where and what controls its production; and, what are the physical properties of fibrin and its relation to embolization? Upon the physiologic variations of thromboplastin, fibrinogen and fibrin and their quantitative interrelations depend the clinical types of the fibrinogen-fibrin conversion syndrome. The designation of this condition is unsatisfactory as at least eleven terms are in use. The appellation "The Fibrinogen-Fibrin Conversion Syndrome" is suggested.

SURGERY IN HEMOPHILIACS WITH SPECIAL REFERENCE TO THE CENTRAL NERVOUS SYSTEM. R. K. JONES AND R. S. KNIGHTON. Ann. Surg. 144:1029, 1956.

A review of the literature concerning hemophiliacs, with lesions of the central nervous system requiring surgical intervention, together with three cases of our own,

is presented. Our cases were (1) Epidural clot over the lower cervical spinal cord requiring laminectomy, (2) Subdural right hematoma with left hemiparesis, (3) Hematoma in right posterior frontal region of the brain. A surgical technic for reducing operative and postoperative hemorrhage in hemophiliacs is suggested in which operative sites are exteriorized so that local measures to control hemorrhage may be applied.

FUNGAL DISEASES IN A GENERAL HOSPITAL; A STUDY OF 88 PATIENTS. J. D. KEYE, JR., AND W. E. MAGEE. Am. J. Clin. Path. 26:1235, 1956.

The clinical records, autopsy protocols, gross and histologic material and microbiologic data from 88 patients with fungal infections were studied. The material was derived from 15,845 consecutive autopsies performed between 1919 and 1954. The data were evaluated by time periods in order to assess the incidence since the introduction of antibiotic therapy, cortisone, etc., and to evaluate the significance of these fungal infections. Secondary fungal infections of varying severity were noted to have increased significantly since 1947. These infections had a definite adverse of hematologic disorders were noted to be most susceptible to secondary fungal infections.

DIAGNOSIS AND TREATMENT OF EOSINOPHILIC GRANULOMA OF SKULL. R. S. KNIGHTON AND J. D. FOX. J.A.M.A. 162:1294, 1956.

Since 1952, we have seen five cases of eosinophilic granuloma of the skull. It is important to consider the possibility that this disease exists when there is any localized tenderness of the scalp or any lytic lesion of the skull. Since eosinophilic granuloma of the skull is frequently solitary and benign and carries a good prognosis, accurate diagnosis should be made by surgical biopsy, with removal of a specimen large enough for microscopic examination. The treatment is uniformly successful with roentgen therapy. Usually, a course of six exposures of 200 r in air is sufficient. The patient's scalp pain is relieved immediately after biopsy and irradiation. The regrowth of the bone of the cranium is usually demonstrated roentgenographically within six months.

AMPUTEES IN INDUSTRY. CHARLES LONG, II. Arch. Phys. Med. 37:766, 1956.

A worker is judged and placed in industry on the basis of his ability for a certain job. His inability to do other jobs is completely irrelevant. In evaluating the disabled person for job placement this primary principle should be kept foremost in mind. At the annual meeting of the American Congress of Physical Medicine and Rehabilitation in 1955, I presented a film entitled "Amputees In Industry." This film was a documentary case history study of five amputees, showing in each case the amputation stump, the prosthesis, and finally the patient at work in industry. The five patients shown in the film are (1) Bilateral Below-Elbow Amputation, (2) Bilateral Above-Knee Amputation, (3) Unilateral Above-Elbow Amputation, (4) Unilateral Below-Knee Amputation, and (5) Unilateral Below-Elbow Amputation. These patients, representative of a large group of such amputees, were selected for a documentary film designed primarily to demonstrate to the trained observer the details of operation of prostheses in industry. The film is obtainable for loan through C. Leslie Mitchell, M.D. Division of Orthopedic Surgery.

***COMBINED TRACER AND VACUUM TECHNOLOGY FOR THE STUDY OF MICRO-WEIGHT VACUUM DISTILLATIONS OF METALS WITH W^{185}, CR^{51} AND AU^{198}. L. E. PREUSS. IN VACUUM SYMPOSIUM TRANSACTIONS. SECTION ON FUNDAMENTAL DEVELOPMENTS IN VACUUM RESEARCH, COMMITTEE ON VACUUM TECHNIQUES, July 1956, p. 7.**

The vacuum distillation technique involving crucible charges of small total mass for purposes such as shadowing in electron microscopy has attained some degree of importance. Quantitative study of this phenomena as it is effected by variables such as the degree of vacuum or the distillation temperature is made difficult by the micro masses used (as low as .1 mg) and the extremely tenuous, resultant condensed metal films which defy conventional quantitative determinations. Thickness of the condensates studied was of the order of one angstrom. Radioactive tracer methodology can be shown to display a useful sensitivity in the assay of the films resulting from the microdistillation process. Tracer assay limits are shown to exceed, by a factor of 10^6, the limits ordinarily found in a coherent metal film. Distilland deflection, as a function of pressure, is studied by gross and micro assay and is shown by the tracer technic to interfere with perfect geometrical shadowing.

An outline is made of the potentially useful synthetic isotopes for vacuum tracer studies. Rules and limits for selection of isotopic qualities in experimental design are outlined. Some simple relations covering experimental activity levels are discussed, (e.g.; $C=D \cdot E$). **Requisites for target material for special pile irradiation are explained. The experimental method used for this film thickness determination is derived and some examples of dispersion patterns and thin film determination are given.

The tracer technic is used here to elucidate some phenomena of the shadowing principle in vacuum distillation. Microdensitometry, autoradiography, electron microscopy, visual assay and calibration by the radioactive counting system all develop correlative results.

Some additional applications for the tracer tool in vacuum studies are outlined. These include: vapor pressure studies, investigation of pumping mechanisms, fractional distillation of alloys, pump back streaming and trapping phenomena, determination of absorbed and adsorbed vacuum contaminants, activation analysis of trace contaminants, etc.

Health physics aspects and certain essentials of the vacuum tracer methodology are explained in detail. A summary is made of the problems, errors, and applications of such tracer assays.

**C=microcuries of total tracer.
$D=(d^1 \cdot d^2)$, where:
d^1=experimental dilution through distillation.
d^2=dilution in final radioactive assay preparation.
E=detector efficiency (expressed in terms of activity units per arbitrary count rate response,)

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*From Edsel B. Ford Institute For Medical Research.

*MODULAR CAVE FOR STORING RADIOACTIVE METAL PARTICLES. L. E. PREUSS. Nucleonics 14:111, Nov. 1956.

A unique lead shield for inventoried storage of radioactive Cr^{51} nodules, Au^{198} foil and W^{185} wire is described. It consists of a ¾" lead walled, rectangular, box shield with dimensions of 2¼" x 4" x 8". Six drawers in horizontal array open on one 2¼" x 8" face. Each contains numbered receptacles for separate storage of small radioactive metal fragments. Excessive dosage during loading is obviated by a movable lead nodule which provides a shielding tunnel accommodating one drawer. Lucite drawer bodies which are easily machined to any shape are described. Gamma ray dosage, from metallic Au^{198} foil, to the operator's hands has been reduced to two to four percent of that from the unshielded source at the shield surface. Dosage has been reduced by about 95 percent during the loading and unloading procedure, when contrasted with the single lead keg storage system previously used.

PRIMARY ADENOCARCINOMA OF THE VERMIFORM APPENDIX. J. C. SIERACKI AND H. TESLUK. Cancer 9:997, 1956.

The authors report 8 cases of primary invasive carcinoma of the appendix and review the literature of the previously reported cases in which they found 42 invasive and 10 intramucosal primary cancers. The difference in prognosis of the intramucosal and invasive tumor and the need for early radical therapy in the latter is stressed.

*STUDIES ON SUCCINIC DEHYDROGENASE. II. ISOLATION AND PROPERTIES OF THE DEHYDROGENASE FROM BEEF HEART. T. P. SINGER, E. B. KEARNEY AND P. BERNATH. J. Biol. Chem. 223:599, 1956.

1. Succinic dehydrogenase has been isolated from beef heart mitochondria as a soluble protein in a state approaching homogeneity by physico-chemical criteria. The over-all purification is about 100-fold compared with a mitochondrial acetone powder.

2. The enzyme is a ferroflavoprotein containing 4 atoms of ferrous (non-hemin) iron and a mole of flavin per mole of protein (200,000[0] gm.). The dehydrogenase may be isolated from aged starting material with 2 atoms of iron per mole and half the specific activity.

3. Among the common electron acceptors, only the following function with the dehydrogenase, at the relative rates indicated in parentheses: phenazine methosulfate (100), ferricyanide (39), O_2 (0.02). The first two of these acceptors react via the iron moieties, whereas O_2 seems to react directly with the flavin.

4. The Qo_2 has been measured as 20,000 and the turnover number as 3000 under the standard assay conditions.

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*From Edsel B. Ford Institute For Medical Research.

5. The properties of the isolated dehydrogenase agree with those previously described for mitochondrial and other particulate preparations of the enzyme, except for properties related to the absence of contaminating hemoproteins. At 38° the pH optimum is 7.7; the Km for succinate is 1.3 x 10^{-3}M at 38° and 5.2 x 10^{-4}M at 21°. Oxalacetate, malonate, and fumarate are competitive inhibitors. Antimycin A and BAL do not inhibit the dehydrogenase. The dehydrogenase is highly sensitive to sulfhydryl reagents, p-chloromercuribenzoate inhibiting it in a reversible manner and the substrate protecting the enzyme from this type of inhibition.

THE CAUSES OF LATE FAILURES IN GRAFTING THERAPY OF PERIPHERAL OCCLUSIVE ARTERIAL DISEASE. D. E. SZILAGYI, J. G. WHITCOMB, AND R. F. SMITH. Ann. Surg. 144:611, 1956.

With a view to identifying the causative factors in the loss of function of formerly open grafts after grafting operations for peripheral (aortoiliac and femoro-popliteal) occlusive arterial disease the postoperative course of 120 such operations was reviewed and analyzed. Twenty-three or 19.1 per cent of the grafts became occluded immediately after operation. The remaining 97 grafts were followed clinically and angiographically. During the subsequent 33 months 21 more grafts lost their function. Seven of them were re-explored and six of the re-explored grafts were biopsied. From the evidence obtained by these studies the most common cause of late graft failure was the extent and severity of the preexisting arterial disease either through postoperative progression or owing to incomplete excision. Although technical variations in the type of graft placement and technique of anastomosis did not seem to be the primary cause of the failures, the technical superiority of procedures utilizing end-to-side distal anastomosis was confirmed, and collateral evidence suggested that this type of anastomosis may delay narrowing near the suture line. Occlusions the cause of which was traced to intrinsic defects in the grafts were uncommon but in a considerable number of cases (17 per cent) progressive angiographic changes were noted in the arterial substitutes that may in time lead to occlusion.

REPLACEMENT OF LONG AND NARROW ARTERIAL SEGMENTS; AN EXPERIMENTAL STUDY OF HETEROGRAFTS AND SEAMLESS WOVEN NYLON AND TEFLON PROSTHESES. D. E. SZILAGYI, C. P. SHONNARD, J. LOPEZ Y. LOPEZ AND N. P. D. SMYTH. Surgery 40:1043, 1956.

Segments, 18 to 24 cm. long and 8 to 10 mm. in diameter, of lyophilized, chemically sterilized bovine heterograft, and of seamless woven tubes of teflon, bleached teflon, and nylon were implanted in dogs and observed for periods of from 2 weeks to 13 months. The heterografts showed a varying and capricious behavior, about one-half of the implants yielding satisfactory results, about one-third rupturing, and the remainder undergoing moderate to advanced degenerative changes. During the periods of observation, prostheses of nylon, teflon, and bleached teflon of the stated

dimensions proved to be satisfactory arterial substitutes. The few failures observed with these replacements appeared to be caused not by the unfavorable biologic behavior of the given plastic but rather by minor and virtually unavoidable technical errors that resulted in various degrees of wrinkling. Thus the importance of the lack of elasticity of these plastic prostheses that render the accuracy of their insertion a critical factor is again emphasized. On account of the minimal tissue reaction it elicits, as well as owing to its nonwettale and durable qualities, the seamless teflon prosthesis offers distinct advantages as a vascular substitute.

EXPERIMENTAL STUDIES ON INTERSTITIAL INJECTION OF RADIOACTIVE COLLOIDAL GOLD (Au^{198}). A. H. VELDHUIS, L. A. SWINEHART, L. E. PREUSS, AND C. P. HODGKINSON. Surg., Gynec. & Obst. 103:539, 1956.

The cure of metastatic cancer is a major challenge to modern medicine. Because the etiology is unknown, we have been forced to treat cancer with only limited success, by surgical extirpation, radiation therapy, or a combination of the two. Under trial are various chemicals, but the results have not been encouraging. Early diagnosis and destruction of the primary tumor and the immediate lymphatics constitute the rational limits of ideal modern therapy. If improvement in survival is to be achieved the diagnosis must be made more promptly, the surgery must be more radical, and radiation therapy more effective. New modalities of therapy are objects of a never ending search. The following protocol for laboratory investigation was adopted. Rabbits weighing between 3,600 and 4,500 grams were used. The site selected for injection was the left inferior thoracic mammary gland. Injections were made under sodium pentothal anesthesia. The breast areas were shaved and painted with 1 per cent hexachlorometacresol solution. The project was divided into three phases. The first phase was characterized by the injection of 4 per cent direct sky blue colloidal dye solution; the second phase, by injection of nonradioactive colloidal gold solution with and without hyaluronidase solution; and the third, by injection of Au^{198}. The investigation showed that the maximum radiation was delivered to the regional lymph nodes. The concentration of radioactive gold in the nodes on the basis of calculated dose indicated a new order of magnitude in terms of radiation dosage. Examinations of the sections of lymph nodes revealed micropathologic changes which were more pronounced than were produced by external radiation. The rate of migration was sufficiently rapid to minimize severe local reaction at the site of injection. The therapeutic use of radioactive gold would seem to be quite safe. A minimum amount of radiation was delivered to the spleen, liver and kidney. Patients under therapy and laboratory animals have shown few untoward effects. The greatest hazard to personnel in the handling of radioactive gold occurs at the time of injection.